Archives of Dermatology and Syphilology

VOLUME 57 MAY 1948 NUMBER 5

COPYRIGHT, 1948, BY THE AMERICAN MEDICAL ASSOCIATION

# STEROID HORMONES

## Metabolic Studies in Dermatomyositis, Lupus Erythematosus and Polymorphic Light-Sensitive Eruptions

*JOHN H. LAMB, M.D.
EVERETT S. LAIN, M.D.
CORINNE KEATY, Ph.D
AND
ARTHUR HELLBAUM, M.D., Ph.D.
OKLAHOMA CITY

NUMEROUS observations point to a relationship between the steroid hormones and certain dermatologic disorders. This is particularly true in certain conditions associated with profound systemic and metabolic changes. Significant sex incidences are common.[1] Cutaneous sensitivity to allergens has been reported to have its peak at the time of greatest estrogen deprivations in women.[2] Furthermore, the correlation of the time of onset of certain cutaneous diseases, exacerbations or remissions with epochs of life during which hormonal balances are undergoing change is significant. Sterilization in women is known to affect the course of some of these diseases.[3]

Hormonal determinations have been largely confined to the study of acne.[4] Various methods have been employed in these de-

---

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June 2, 1947.

This study has been aided in part by grants from the Oklahoma Medical Research Foundation and the National Research Council.

From the Departments of Dermatology and Syphilology and Pharmacology, School of Medicine of the University of Oklahoma, Oklahoma City.

1. (*a*) Rose, E., and Pillsbury, D. N.: Lupus Erythematosus (Erythematodes) and Ovarian Function: Observations on Possible Relationship, with Report of Six Cases, Ann. Int. Med. **21**:1022, 1944. (*b*) Sarateanu, F.: Sommer Prurigo Hutchinson, Zentralbl. f. Haut- u. Geschlechtskr. **60**:240, 1938.

2. Hansen-Prüss, O. C., and Raymond, R.: Skin, Reactivity During the Menstrual Cycle, J. Clin. Endocrinol. **2**:161, 1942.

3. Rose and Pillsbury.[1a] Cedarcreutz, A.: Impetigo Herpetiformis: Serious Case Definitely Cured After Radiographic Castration, Acta dermat. venereol. **20**:-430, 1939. Johnson, J. B., and Mazique, E. C.: Disseminate Lupus Erythematodes Unsuccessfully Treated with Penicillin: Roentgen Ray Castration and Serum Albumin, Ann. Int. Med. **25**:559, 1946.

4. Wile, U. J.; Snow, J. S., and Bradbury, J. T.: Studies on Sex Hormones in Acne: II. Urinary Excretion of Androgenic and Estrogenic Substances, Arch. Dermat.

*(Footnotes continued on next page)*

terminations, in most instances making it difficult to compare the results quantitatively. Methods in use at the present time for estrogen determinations do not consider quantitatively or qualitatively the various types of estrogens and, thus, are not reliable indexes of the functional estrogen level in the body.

A limited number of studies have been made in other dermatologic disorders. In 1 case of lupus erythematosus in a male patient, Rose and Pillsbury[1a] observed a reduced androgen-estrogen ratio and an increased secretion of pituitary gonadotropin. Hamblen[5] has reported the association of recurrent premenstrual dermatosis with elevated pregnandiol excretion in 1 patient.

The empiric use of hormones in the treatment of a variety of cutaneous diseases has, in most instances, yielded conflicting results. However, the use of corpus luteum in the treatment of herpes gestationis has, in most of the single cases, been of benefit. Gilman[6] has used corpus luteum in herpes gestationis with toxemia of pregnancy, with resultant remission. Sechi[7] concluded that this disease is due to a disturbed production of progestin. However, estrogens, including progesterone were without effect in the case described by Turner and Zakon.[8] Lichen simplex during artificial menopause[9] and keratoderma climactericum[10] have both been reported as responding favorably to diethylstilbestrol. Natural and synthetic estrogens have been used with success in the treatment of photosensitive eruptions. Goldberg,[11] Lancaster,[12] Selisky,[13] Epstein[14] and Hadley[15] have em-

---

& Syph. **39**:200 (Feb.) 1939. Cornbleet, T., and Barnes, B.: The Hormones and Acne Vulgaris: I. Urinary Assay and Therapeutic Use of Androgen, ibid. **40**:249 (Aug) 1939. McCarthy, L., and Hunter, O. B.: Failure of Therapy with Grandular Preparations in Acne Vulgaris, ibid. **35**:211 (Feb.) 1937.

5. Hamblen, E. C.: A Syndrome Characterized by Premenstrual Dermatosis, Polyhypermenorrhea, Dysmenorrhea, Menstrual Headache and an Increased Urinary Excretion of Sodium Pregnandiol Glucuronide, Endocrinology **28**:269, 1939.

6. Gilman, R. L., in discussion on Stokes, J. H.: Herpes Gestationis, Arch. Dermat. & Syph. **27**:1003 (June) 1933.

7. Sechi, E.: Herpes gestationis, Gior. ital. di dermat. e sif. **73**:1353, 1932.

8. Turner, S. J., and Zakon, S. J.: Herpes Gestationis, Am. J. Obst. & Gynec. **41**:525, 1941.

9. Semon, H. C.: Lichen Simplex Controlled by Stilbestrol, Brit. J. Dermat. **54**:181, 1942.

10. Lynch, W. F.: Keratodermia Climactericum (Haxthausen), Arch. Dermat. & Syph. **48**:270 (Sept.) 1943.

11. Goldberg, N. M.: Climacteric Hypersensitiveness to Sun and Effort: Treatment with Follicular Hormone (Theelin), J. Allergy **6**:298, 1935.

12. Lancaster, A. H.: Estrogenic Hormone Therapy in Sunlight Eruptions of the Female, South. M. J. **32**:495, 1939.

13. Selisky, A. B.: Neue Behandlungsmethode von Lichtdermatosen, Dermat. Wchnschr. **101**:299, 1935.

ployed estrone ("theelin") in oil or aqueous solution in photosensitive eruptions in female patients. Zugerman and Gross[16] have reported recovery from bullous lichen planus after the administration of estrogen.

### DERMATOMYOSITIS

Dowling and Griffiths[17] have extensively studied the metabolic aspects of dermatomyositis. These workers have pointed out that in both scleroderma and dermatomyositis similar metabolic changes are present, many of which may also be observed in thyrotoxicosis, and thyroid changes were observed in a majority of their patients. Creatine excretion in the two former conditions may exceed 600 mg. in twenty-four hours. There is decided daily fluctuation in total creatinine from low to high values, although in severer stages of the diseases, there is a tendency, in general, to low creatinine excretion. Carbohydrate tolerance may be decreased, and the peripheral action of insulin may be impaired in some cases. However, in a series of 9 cases, Jaeger[18] was unable to demonstrate any change in the peripheral action of insulin. Edema in both scleroderma and dermatomyositis is generally the first symptom and may persist for years. Muscular weakness and tenderness are the predominating symptoms. O'Leary and Waisman[19] have comprehensively described the diverse forms assumed by the cutaneous lesions in dermatomyositis.

There is evidence that the muscular changes in dermatomyositis are associated with processes involving protein metabolism. The edema is suggestive. Relatively severe creatinuria and daily fluctuations in creatinine excretion are generally constant observations. The destructive changes seen in the biopsy of muscle in dermatomyositis and scleroderma may or may not precede the physiologic change in myotropic activity and metabolism. Physiologic derangement is thought to precede visible structural change in other muscular dystrophies.

---

14. Epstein, S.: I. Studies in Abnormal Human Sensitivity to Light, J. Invest. Dermat. **5**:187, 1942.

15. Hadley, H.: Urticaria Solaris, Urol. & Cutan. Rev. **45**:406, 1941.

16. Zugerman, I., and Gross, P. P.: A Case Report of Bullous Lichen Planus with Recovery Following the Use of Estrogenic Hormone, Pennsylvania M. J. **47**: 571, 1944.

17. Dowling, G. B., and Griffiths, W. J.: Dermatomyositis and Progressive Scleroderma, Lancet **1**:1424, 1939.

18. Jaeger, B. V., and Grossman, L. A.: Dermatomyositis, Arch. Int. Med **73**:271 (April) 1944.

19. O'Leary, P. A., and Waisman, M.: Dermatomyositis: A Study of Forty Cases, Arch. Dermat. & Syph. **41**:1001 (June) 1940.

The relationship of steroids to the retention and release of creatine from tissues is not as yet understood, but there is considerable evidence that such a relationship exists.

Four patients with dermatomyositis have been studied with reference to creatine tolerance and creatine-creatinine and 17-ketosteroid excretion. Determinations were made on complete twenty-four hour urinary specimens. Creatine-creatinine excretion was determined by the method of Folin, using the Klett photoelectric colorimeter. Creatine tolerance tests were carried out according to the method of Richardson and Shorr.[20] Excretion of 17-ketosteroid was determined by the method of Robbie and Gibson.[21]

## REPORT OF CASES

*Case* 1.—F. C., a white woman, aged 32, presented a history of prolonged and profuse menstrual bleeding for several years prior to onset of the disease. Several months before the symptoms appeared, the patient had lost about 30 pounds (about 13.6 Kg.) on a reducing diet. A diagnosis of contact dermatitis had been made previously.

On examination the patient showed edema and erythema of the face and eyelids, with an erythematous exfoliative eruption on the extremities, chest, back and arms. Scaly erythematous lichenoid areas were present over the dorsa of the fingers. The skin showed areas of scleroderma, and there was generalized edema. Muscular weakness and tenderness, as well as dysphagia, were also present. Microscopic examination of muscle tissue showed edema, loss of striations and moderate inflammatory changes. Fever therapy (typhoid) and a trial of penicillin resulted in temporary improvement.

Since Swartz[22] had reported clinical improvement in dermatomyositis following treatment with amino acids and testosterone propionate, 25 mg. of this hormone was administered twice weekly. There was loss of edema and improvement in muscular strength, but the eruption was not significantly improved. After several months profuse and prolonged menstrual bleeding recurred, accompanied with muscular symptoms and edema.

Roentgen radiation of the ovaries was followed by temporary interruption of the menstrual cycle. The muscular symptoms appeared to be at least arrested, but the tissues were fibrosed and considerable contracture remained. Cutaneous lesions resembling poikiloderma were present on the entire body. There was little change for a period of one year. Reestablishment of ovarian function, with prolonged menstrual periods, was accompanied with muscular weakness. For a period of four months the patient was without treatment. During this time serum proteins were 8.6 mg. The albumin-globulin ratio was reversed (3.5 to 5.4 mg.), with increased globulin. A trial of protein hydrolysate[23] and progesterone was without noticeable effect. The patient was given permanent sterilization with roentgen rays, and treat-

20. Richardson, H. B., and Shorr, E.: The Relation of the Thyroid Gland to Graves' Disease, M. Clin. North America, **18**:791, 1934.

21. Robbie, W. A., and Gibson, R. B.: Rapid Clinical Determination of Urinary 17-Ketosteroids, J. Clin. Endocrinol. **3**:200, 1943.

22. Swartz, J. H., in Discussion of Dermatomyositis at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., June 21, 1944.

ment with testosterone and protein hydrolysate was reinstituted. In spite of menopausal difficulties, as of the time of writing she was slowly gaining in strength. Throughout treatment, creatine-creatinine levels were not greatly affected and retention of exogenous creatine was not improved significantly except during administration of progesterone.

*Case* 2.—J. F., a white woman, aged 44, gave a history of prolonged and profuse menstrual bleeding prior to hysterectomy and unilateral ovariectomy. Operation

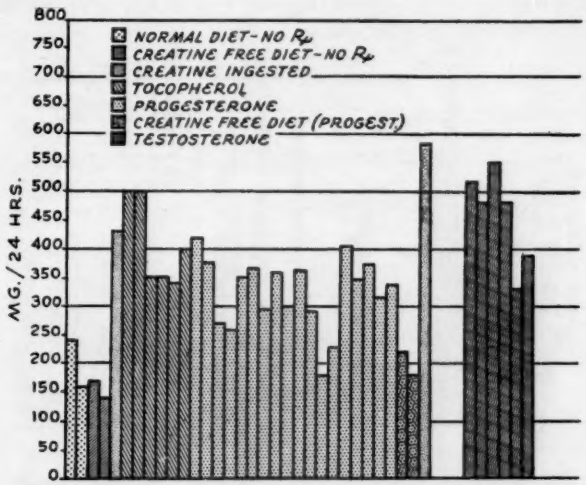



FIG. 1 (case 1).—Thirty-eight twenty-four hour creatine determinations, including creatine tolerance tests, without treatment and with treatment (progesterone).

TABLE 1.—*Creatine-Creatinine Excretion, Creatine Tolerance, and 17-Ketosteroid Excretion in a Patient (F. C.) with Dermatomyositis*

| Medicament* | Average total Creatinine (Mg./24 Hr.) | Average Creatine (Mg./24 Hr.) | Excretion after 1 Gm. Creatine Ingested (Mg./24 Hr.) | Average 17-Ketosteroid (Mg./24 Hr.) |
|---|---|---|---|---|
| None | 293.43 | 200.00 | 426.00 | 7.611 |
| Progesterone | 459.77 | 362.58 | 573.76 | 8.320 |
| Testosterone propionate | 1,206.90 | 533.45 | | |

*Sterilization necessitated discontinuation of studies with testosterone.

was performed six months after the appearance of symptoms of dermatomyositis. Moderate improvement followed operation, but there was exacerbation four months later, at which time the patient was first seen by us. The eruption involved the upper part of the body, including the scalp and arms. Bright red erythema, more intense on the areas exposed to light, with exfoliation and thickening of the skin, was present. Also present was beginning alopecia, edema of the face and eyelids, great muscular weakness and tenderness of the muscle, accompanied with severe

23. The Maltine Company, Mead Johnson and Company and Eli Lilly and Company supplied the protein hydrolysates used in these studies.

creatinuria. Extracts of liver and testosterone propionate, 10 mg. twice weekly for three months, was administered. There was decided clinical improvement and increased creatine retention. At this time treatment with protein hydrolysate was begun (60 to 80 Gm. protein equivalent daily). Improvement continued, with subsidence of the edema and muscular symptoms. There was some improvement in the cutaneous lesions. Microscopic examination of a muscle specimen showed some loss of striations, with clusters of mononuclear cells within the interstitial fibrous tissue between the muscle bundles. Here these cells were arranged primarily around, or

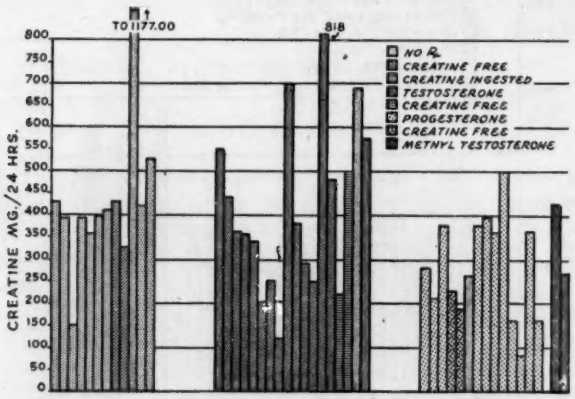



FIG. 2 (case 2).—Forty-six twenty-four hour creatine determinations, including creatine tolerance tests, without treatment and with treatment (progesterone and testosterone).

TABLE 2.—*Creatine-Creatinine Excretion, Creatine Tolerance and 17-Ketosteroid Excretion in a Patient (J. F.) with Dermatomyositis*

| Medicament | Average total Creatinine (Mg./24 Hr.) | Average Creatine (Mg./24 Hr.) | Excretion after 1 Gm. of Creatine (Mg./24 Hr.) | Average 17-Ketosteroid (Mg./24 Hr.) |
|---|---|---|---|---|
| None | 623.88 | 341.34 | 1,177.00 | 4.894 |
| Progesterone | 577.77 | 287.87 | 261.00 | 5.112 |
| Testosterone propionate | 642.64 | 395.75 | 680.68 | 7.100 |

adjacent to, small blood vessels. This inflammatory reaction was not great, but when considered in conjunction with the apparent loss of, or at least reduction in, the striation of the muscle, it was indicative of myositis. These changes, in view of the similar, yet minimal, observations within the dermis, were reported as compatible with dermatomyositis. Treatment with testosterone propionate, 10 mg. twice weekly, was continued for three months. Improvement in muscular strength was rapid. This was followed by two months of treatment with progesterone, 10 mg. daily. Creatine retention was further increased. Protein hydrolysate and extract of liver were administered throughout the periods of treatment. Levels of creatine and 17-ketosteroid during periods of treatment and without treatment are shown in table 2.

Daily fluctuation in creatinine persisted during both periods of treatment. Both progesterone and testeosterone had a decided effect on the ability to retain exogenous creatine. The endogenous creatinuria was decreased, but not completely suppressed. Regrowth of hair and eyebrows, loss of edema, improvement of the eruption and increased muscular strength resulted.

*Case* 3.—N. F., a white woman, aged 75, had a noncontributory history except for old recurrent pyelitis. Muscular weakness and pain had been present for a year. The eruption had been late in appearing, although the edema had been apparent for several months. On examination, the patient showed an erythematous slightly

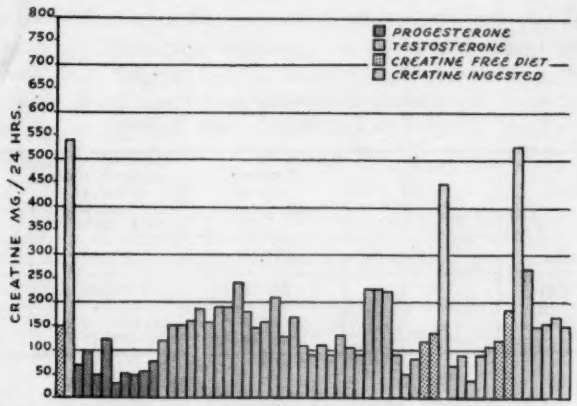



FIG. 3 (case 3).—Fifty-five twenty-four hour creatine determinations, including creatine tolerance tests, without treatment and with treatment (progesterone and testosterone).

TABLE 3.—*Creatine-Creatinine Excretion, Creatine Tolerance and 17-Ketosteroid Excretion in a Patient (N. F.) with Dermatomyositis*

| Medicament | Average total Creatinine (Mg./24 Hr.) | Average Creatine (Mg./24 Hr.) | Excretion after Ingestion of 1 Gm. of Creatine (Mg./24 Hr.) | Average 17-Ketosteroid (Mg./24 Hr.) |
|---|---|---|---|---|
| None | 290.11 | 107.77 | 543.48 | 0.3 |
| Progesterone | 252.80 | 70.39 | | 1.127 |
| Testosterone propionate | 230.03 | 156.39 | 491.58 | 1.222 |

Average creatine, creatinine and 17-ketosteroid excretion in 3 patients are shown in table 4.

scaly eruption on the face, with edema and telangiectasis of the eyelids and papular erythematous lichenoid lesions on the dorsa of the fingers. The erythema showed a line of demarcation at the "V" of the neck. The chest, arms and legs were erythematous, and the skin was edematous. There was moderate creatinuria with decided muscular pain and weakness. The patient was unable to feed herself or to walk. The report of a biopsy of muscle at this time was of myositis, atrophy and waxy change. Striations were occasionally absent or dim, with variations in width. Progesterone, 10 mg. daily, was administered for twelve days. There was little clinical improvement. The patient was then given testosterone propionate, 25 mg. twice

a week, extract of liver, amino acids and B vitamins. After twenty-eight days she was able to walk with assistance and feed herself. There was considerable improvement in the dermatitis. Extract of liver was withdrawn after three months. This was followed by a violent exacerbation of the cutaneous lesions, without any change in the now greatly increased muscular strength and volume. It is of interest that this exacerbation was associated with a recurrence of pyelitis. A dramatic remission of the cutaneous lesions followed intravenous injection of pyridoxine, 1 mg. twice a week. A second attack of pyelitis has been accompanied with recurrence of cutaneous lesions.

Creatine-creatinine and 17-ketosteroid excretion during this period are shown in table 3. Creatinuria in this patient had never been as severe as in the other 2 cases. Progesterone did not significantly depress the creatinuria or affect retention of exogenous creatine. Testosterone propionate, however, moderately increased the ability to retain ingested creatine.

TABLE 4.—*Effect of Testosterone Propionate and Progesterone on Creatine Metabolism in Dermatomyositis (3 Cases)*

| Medicament | Average Total Creatinine (Mg./24 Hr.) | Average Creatine (Mg./24 Hr.) | Excretion after ingestion of 1 Gm. of Creatine (Mg./24 Hr.) | Average 17-Ketosteroid (Mg./24 Hr.) |
|---|---|---|---|---|
| None | 402.47 | 219.55 | 715.49 | 4.268 |
| Progesterone | 430.11 | 240.28 | 417.38 | 4.853(5.0) |
| Testosterone propionate | 693.05 | 262.53 | 586.13 | 4.131 |

The fourth patient received implants of testosterone propionate pellets.[24]

*Case* 4.—F. G., a 9 year old white boy, was admitted to Children's Hospital complaining of loss of weight, general muscular weakness, pain, facial edema and an erythematous eruption on both cheeks. There was also a mottled erythematous eruption on most of the body, with areas of slight exfoliation. He was unable to rise from a supine position; there was moderate contracture of both the elbows and the knees. All muscles, primarily the muscles of the neck, shoulders and hips, felt indurated and were weak and painful on motion. There was mild tenderness on pressure of all muscles. The testicles were undescended; no pubic hair was apparent, and the penis was of normal size for a boy of that age. There was moderate contracture of both knees and both elbows. The blood picture was essentially normal. Total protein was 6.5 mg., with an albumin-globulin ratio of 5.4 to 1.1 mg. The sedimentation rate (Wintrobe) was 50 mm. in one hour. There was creatinuria. The electrocardiogram was suggestive of low grade ventricular preponderance on the right side and possibly on the left. Roentgenograms of the upper and lower extremities showed normal bone age. There were osteoporsis and tissue calcification. The spleen was enlarged. Treatment with testosterone propionate (25 mg. twice weekly), protein hydrolysate (100 Gm. daily), extract of liver (1 cc. [5 units] on alternate days), vitamin B complex and ascorbic acid was continued for seven weeks. There was little apparent improvement.

Three 75 mg. pellets of testosterone propionate were implanted subcutaneously in the lower part of the abdomen. Three weeks later the patient was somewhat

24. The Schering Corporation supplied the pellets of testosterone propionate as well as testosterone propionate ("oretone"), and progesterone ("prolution").

improved. He was discharged. Treatment with vitamins and extract of liver, with the addition of 5 mg. of methyl testosterone given orally twice a week, was continued for two months. On readmission the boy was observed to be decidedly improved. Muscular tenderness and stiffness had subsided. There was no edema. The cutaneous lesions were still present, and there was hypertrophy of the penis and a small amount of pubic hair. Contractures were less apparent. Total protein as this time was 7.15 mg., with an albumin-globulin ratio of 5.12 to 2.05. The creatinuria was still persistent. Roentgenographic examination of the pelvis showed little change in calcium deposit. Three more 75 mg. pellets of testosterone were implanted.

The decided clinical improvement effected in patients with dermatomyositis evoked by the administration of testosterone, as evidenced by increased dynametric strength of intact muscle fibers, the apparent arrest of the destructive processes and subsidence of edema, may be explained largely on the basis of the nitrogen-retaining power of the androgen. Improvement in cutaneous lesions may be related to vascular effects: increase in the vascular bed, increase in oxyhemoglobin in the peripheral vessels and known hemopoietic effect of the androgen. It is highly questionable whether there is any restoration of muscle tissue in these patients. The curtailment

TABLE 5.—*Effect of Testosterone Propionate in a Patient (F.G.) with Dermatomyositis*

| Medicament | Average Total Creatinine (Mg./24 Hr.) | Average Preformed Creatinine (Mg./24 Hr.) | Average Creatine (Mg./24 Hr.) | Excretion after Ingestion of 1 Gm. of Creatine (Mg./24 Hr.) | Average 17-Ketosteroids (Mg./24 Hr.) |
|---|---|---|---|---|---|
| None | 360.70 | 87.73 | 272.97 | | 2.392 |
| Testosterone | 217.60 | 60.00 | 157.00 | 308.00 | |

of the excretion of exogenous creatine and a tendency to stabilize creatinine excretion with treatment would indicate improved nitrogen metabolism. It is significant that best results have been obtained in patients in whom the duration of the disease had been comparatively brief. After the permanent sclerotic changes have been effected in the vascular bed and muscular fibrosis established, as in case 1, hormonal therapy was observed to be only moderately effective. It is possible, however, that the changes are arrested.

## LUPUS ERYTHEMATOSUS IN FEMALE SUBJECTS

In 1942, interest in the hormones as related to lupus erythematosus in female patients was stimulated by 2 cases of subacute disease in women 36 and 39 years of age, respectively. Both patients presented a history of severe menometrorrhagia, and because of their general condition it was decided to subject them to roentgen ray sterilization. In both these women there was decided improvement in the lupus erythematosus, indicative of a possible relationship between the resultant hormonal change and the course of the disease.

Contratto and Levine[25] reported a case of disseminated lupus erythematosus in which the patient was treated with roentgen ray sterilization, with improvement for a few days. The patient had pneumonia two days after sterilization and died before any conclusions could be drawn.

25. Contratto, A. V., and Levine, S. A.: Subacute Lupus Disseminatus, New England J. Med. **221**:602, 1939.

Rose and Pillsbury[1a] reported improvement in 3 out of 5 cases after roentgen ray sterilization or surgical castration, and these authors suggested a relationship between ovarian function and disseminated lupus erythematosus.

Curtis[26] used radium to sterilize 2 patients with acute lupus erythematosus; 1 patient had been well for five years at the time of writing.

Studies are now in progress of female patients with the diagnosis of lupus erythematosus. At this time the observations in 13 female patients, are as follows: Ages ranged from 10 to 54 years. Ten of these patients had a history of some disturbance of ovarian function, as evidenced by menorrhagia, low estrogenic vaginal smears, estrogenic or mixed progestational endometria or surgical menopause. The average 17-ketosteroid excretion in these 13 patients was observed to be 6.97 mg. per twenty-four hours (normal values by the method used range from 5 to 15 mg. per twenty-four hours). This average is, therefore, in the lower limits of normality. The average total creatinine in 10 patients was 906.48 mg. per twenty-four hours and creatine 165.50 mg. per twenty-four hours. Seven of these patients have received steroid therapy. In one instance progesterone was observed to control premenstrual exacerbations in chronic discoid lupus erythematosus.

Testosterone propionate given to 5 selected female patients with lupus erythematosus seemed to improve the general well-being of the patients, but difficulty was experienced in continuing treatment because of fears of prolonged use of the male sex hormone by the patients. Two patients showed improvement in the appearance of the lesions; in 1 there was complete disappearance of all cutaneous manifestations of the disease.

Studies are in progress on the use of progesterone in lupus erythematosus in female patients, since it may have the beneficial effects of testosterone without the masculinizing effects.

### LUPUS ERYTHEMATOSUS AND PHOTOSENSITIVE ERUPTIONS IN THE MALE SUBJECTS

The study of hormone levels in male subjects offers a less complicated field of investigation than in female subjects because of the absence of cyclic hormonal fluctuations. Preliminary investigation of creatine-creatinine and 17-ketosteroid excretion has been made in 6 men with photosensitive eruptions,[27] in 2 men with chronic discoid lupus erythematosus and in 1 case of acute disseminated lupus erythematosus which terminated in death.

The significant observations in these patients at the time of writing are summarized as follows:

1. The average age of the patients was 43. Five of these were over 40 years of age.

2. In the polymorphic photosensitive group: (*a*) There was moderately low or decided depression of the excretion of urinary 17-ketosteroids. (*b*) There was moderate to severe creatinuria when cutaneous lesions were acute. (*c*) During winter remission, 1 patient who did not have treatment with the steroid hormones was observed to have an elevation of previously low 17-Ketosteroids and an absence of creatinuria which during the acute phase had been severe.

---

26. Curtis, A. C., in discussion on Shaffer, L., and others: Discoid and Disseminate Lupus Erythematosus, Arch. Dermat. & Syph. **54**:467 (Sept.) 1946.

27. Dr. Zola Cooper has given valuable assistance in histologic studies of the photosensitive group of patients.

### HYDROA (VACCINIFORME)

While no detailed studies have been made of hydroa vacciniforme, it is of interest that 2 preadolescent girls with relatively high urinary 17-ketosteroid levels for their age group, were relieved of their photosensitivy with injections of small doses of estrone (aqueous "theelin"), 100 to 200 units.

One 18 year old male patient with seminal insufficiency has been treated for four months with pregnant mare's serum ("gonadogen"), 10 Cartland-Nelson units (approximately 200 international units) daily. Results have been gratifying.

TABLE 6.—*Average Initial Values of Creatine and 17-Ketosteroid Excretion in Male Male Patients With Polymorphic Photosensitive Eruption*

| | |
|---|---|
| Total creatinine (Mg./24 Hr.) | 1,649.87 |
| Creatine (Mg./24 Hr.) | 276.87 |
| 17-Ketosteroid (Mg./24 Hr.) | 4.83(5.0) |

TABLE 7.—*Average Creatinine-Creatine and 17-Ketosteroid Excretion in 2 Treated Male Patients With Polymorphic Photosensitive Eruption*

| Medicament | Total Creatinine (Mg./24 Hr.) | Average Creatine (Mg./24 Hr.) | Average 17-Ketosteroid (Mg./24 Hr.) |
|---|---|---|---|
| Gold compound and extract of liver | 1,308.55 | 128.31 | 5.34 |
| Extract of liver and testosterone propionate | 1,617.83 | 176.83 | 7.400 |
| Extract of liver, testosterone propionate and thyroid | 1,416.84 | 100.11 | 8.890 |

### COMMENT

There are undoubtedly many points of physiologic interaction between amino acid metabolism, the vitamins and hormones. Few of these interrelationships have been clarified.

Creatinuria is present in a number of diverse pathologic conditions and cannot be considered diagnostic. Deranged protein metabolism is evidenced by the constant creatinuria and concomitant muscular changes in dermatomyositis. The role of creatine, as phosphocreatine, itself an important methyl amino acid in reactions concerned with the release of energy in muscle tissue and in phosphorylation, is of significance. Depletion of phosphocreatine, the expulsion of creatine from the muscle tissue and its appearance in the urine results in lowered nitrogen retention with reference to tissue protein. The point or points of interaction between steroid hormones, particularly androgens, and creatine metabolism may lie in the nitrogen-retaining power of the hormone. In this respect, studies of the effects of androgens on creatinuria are suggestive.

The physiologic creatinuria of childhood is paralleled by poor creatine tolerance in both sexes[28] and cannot be abolished by the administration of androgen or chorionic gonadotropin in male patients.[29] Nathanson and his co-workers[30] associate preadolescent creatinuria with 17-ketosteroid levels. There is impairment in creatine retention in men in old age and after castration.[31] Creatine retention has been used as a measure of androgen activity in elderly men of an age at which prostatic difficulties are likely to occur.[32] There are numerous reports of constant creatinuria in castrated men and boys[33] and its depression by the administration of androgen.[34] The male patient with hypogonadism is unable to retain exogenous creatine.[35] In studies of the metabolism of eunuchs treated with testosterone propionate, Kenyon and his associates[36] observed that the hormone exerts significant effects on nitrogen, electrolyte and water balance, evidenced by decreased urinary nitrogen, chloride, potassium and sodium. There was slight decrease in the creatinuria, moderate increase in basal metabolism and increased body weight. Depression in creatine excretion was explained on the basis of salt and water storage. Creatinine values were not seriously affected. Essentially the same observations were reported for normal men and women receiving testosterone propionate.[37] However, Beard and his co-workers[38]

28. Krause, R. A.: On Age and Metabolism and on the Significance of the Excretion of Creatine, Quart. J. Exper. Physiol. **7**:87, 1914.

29. Duckworth, D. A.: Creatine Retention Capacity of Boys in Relation to Androgenic Function, J. Clin. Endocrinal. **2**:13, 1942.

30. Nathanson, I. T.; Miller, R. B.; Towne, L. E., and Aub, J. C.; The Close Correlation of Androgen and Creatinine Excretion in Normal Children, Endocrinology **28**:866, 1941.

31. Remen, L.: Ueber den Abbau parenteral Zugeführten Kreatins-bei Erwachsenen mit erloschener Geschlechtsfunktion, Ztschr. f. d. ges. exper. Med. **86**:288, 1932; Kreatinurie and Ovarialfunktion, ibid. **81**:223, 1932.

32. Sutton, M. M.: Creatine-Creatinine Metabolism in Older Patients with Prostatic Enlargement, J. Clin. Endocrinol. **1**:882, 1941.

33. Read, B. E.: The Metabolism of the Eunuch, J. Biol. Chem. **46**:281, 1921.

34. Buhler, F.: Ueber den Einfluss der Sexualhormone auf den Kreatinstoffwechsel, Ztschr. f. d. ges. exper. Med. **86**:638, 1933.

35. Schittenhelm, A., and Bühler, F.: Die Spontankreatinurie bei innersekretorischen Störungen, ihr Vorkommen und ihr diagnostischer Wert, Ztschr. f. d. ges. exper. Med. **95**:18, 1934.

36. Kenyon, A. T.; Sandiford, I; Bryan, A. H.; Knowlton, K. and Koch, F. C.: The Effects of Testosterone Proprionate on Nitrogen, Electrolyte, Water Balance and Energy Metabolism in Eunuchoidism, Endocrinology **23**:135, 1938.

37. Kenyon, A. T.; Knowlton, K.; Sandiford, I.; Koch, F. C., and Lowtwin, G.: A Comparative Study of the Metabolic Effects of Testosterone Propionate in Normal Men and Women in Eunuchoidism, Endocrinology **26**:26, 1940.

38. Beard, H. H.; Espenan, J. K.; Koren, A. L., and Pizzolato, P.: Creatine-Creatinine Metabolism and the Hormones, Endocrinology **29**:762, 1941.

observed that injection of water or isotonic solution of sodium chloride evoked creatinuria in human beings and in rats. Chorionic gonadotropin, in stimulating testicular secretion of the androgen, was observed to have the same effects as administration of androgen, without causing any significant increase in excretion of 17-ketosteroids.[39] Similarly, in experiments with animals, castrated and normal male rats were observed to retain administered exogenous creatine after the injection of testosterone propionate.[40] Steinach and his associates[41] stated that excretion of urinary creatine of more than 10 per cent of ingested creatine is indicative of gonadal failure in human subjects.

While no single vitamin can be linked with amino acid metabolism, vitamin C, as far as the available information goes, is intimately associated with these processes. From the standpoint of the pathologist, its function includes, among others, the synthesis and maintenance of collagen, the chief protein of all connective tissues of the body, including that of the vascular endothelium.[42] This concept is supported by the work on scorbutic tissues. However, results of in vitro studies of collagen formation have not been in agreement with this generally accepted function of the vitamin.[43] Apparently the relationship of vitamin C to elastin and the elastic tissues has not been investigated.

Ascorbic acid may have a role in protein degradation.[44] It has been observed to deaminize and decarboxilize a series of amino acids[45]

---

39. Kenyon, A. T.; Knowlton, K.; Lotwin, G.; Munson, P. L.; Johnson, C. D., and Koch, F. C.: A Comparison of the Metabolic Effects of Testosterone Propionate with Those of Chorionic Gonadotropin, J. Clin. Endocrinol. **2**:685, 1942.

40. Coffman, J. R., and Koch, F. C.: Effect of Testosterone Propionate on Creatinuria, Proc. Soc. Exper. Biol. & Med. **42**:779, 1946.

41. von Steinach, E.; Kuhn, H., and Pecznik, O.: Diagnosticher Test für hormonobedingte Störungen der männlicher Sexual Funktion und seine klinische Anwendung, Wien. klin. Wchschr. **49**:388, 1936.

42. Wohlbach, S. B.: Vitamin Deficiency Experimentation as a Research Method in Biology, Science **86**:569, 1937.

43. Hass, G., and McDonald, F.: I. The Production of Collagen in Vitro Under Variable Experimental Conditions, Am. J. Path. **16**:525, 1940.

44. Robertson, W. v. B.; Ropes, M. W., and Bauer, W.: Action of Ascorbic Acid and Hydrogen Peroxide on Collagen and Thymonucleohistone, Proc. Soc. Exper. Biol. & Med. **49**:697, 1942; The Degradation of Mucins and Polysaccharides by Ascorbic Acid and Hydrogen Peroxide, Biochem. J. **35**:903, 1941.

45. Edlbacher, S., and Leuthardt, F.: Die Chemie, Klin. Wchnschr. **12**:1843, 1933.

and to promote the conversion of tyrosine to dopa in the presence of ultraviolet rays.[46]

The significance of these observations, with reference to the altered metabolism of dermatomyositis and lupus erythematosus, is obvious. The collagen changes described by Klemperer and Pollack[47] as involving this substance throughout the body and thereby affecting the vascular structures must be considered as a result of aberrant metabolic processes.

The role of the liver in the degradation of steroids is well known, but many phases of the processes involved are not understood. The use of extract of liver and vitamin B complex in the treatment of dermatomyositis, lupus erythematosus and photosensitive eruptions in some instances has been of benefit and should be mentioned in this respect. The B vitamins have been observed to be related to protein intake.[48] Riboflavin, in particular, has been shown to be related to hepatic function with reference to metabolism of casein.[49] The retention of riboflavin is dependent on protein intake.[50] The reduction, and sometimes the suppression, of creatinuria of normal infants with vitamins $B_1$ and $B_2$ has been explained by Basile and Pecorella[51] on the basis of the glycogen-fixing effect of these vitamins on muscle.

The effects of the products of steroid degradation are not known. From normally secreting gonads (and the adrenal must not be excluded) these are probably produced in a normal liver, uterine endometrium and reticuloendothelial system in quantitatively normal balance. Decreased amounts of the hormone may possibly result in

---

46. Junowicz-Kocholaty, R., and Kocholaty, W.: Arginase, Science **94**:144, 1941.

47. Klemperer, P. and Pollack, A. D.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941.

48. Richter, C. P., and Barelare, B., Jr.: Further Observations on the Carbohydrate, Fat, and Protein Appetite of Vitamin B Deficient Rats, Am. J. Physiol. **127**:199, 1939. Richter, C. P., and Richter, C. D.: The Dependence of the Carbohydrate, Fat and Protein Intake of Rats on the Various Components of the Vitamin B. Complex, ibid. **131**:639, 1941. Elsom, M. C., and Machella, T. E.: Studies of the Vitamins B in the Human Subject: I. The Intake of Thiamine and Its Relation to Other Dietary Constituents in Foods Selected by the Normal Subject, Am. J. Sc. **202**:502, 1941.

49. Kensler, C. J.; Sugiura, K. L.; Young, N. F.; Halter, C. R. and Rhoades, C. P.: Partial Protection of Rats by Riboflavin with Casein Against Liver Cancer Caused by Dimethylaminoazobenzene, Science **92**:300, 1941.

50. Sarett, H. P.; Klein, J. R., and Perlzweig, W. A.: The Effect of Variations in Protein Intake on Urinary Excretion of Riboflavin, Nicotinic Acid, Pyridoxine and Thiamine in Dogs, Federation Proc. **1**:132, 1942.

51. Basile, B., and Pecorella, F.: The Effect of Vitamins on the Renewal of Creatine Compounds in Infants, Pediatria **47**:475, 1939; Chem. Abstr. **35** (pt. 1.): 779, 1940.

production of abnormal amounts of one or several degradation products. If any of these substances can induce any form of sensitivity, it is unknown.

The blood supply of the skin and the deposition of protein in the skin may be related to the action of the steroid hormones. In studies of the castrated human male subject, Edwards, Hamilton, Duntley and Hubert[52] observed that the cutaneous arteriolar bed is smaller than normal and there is a decrease in the amount of oxyhemoglobin. The amount of oxyhemoglobin is increased in the peripheral arteriolar bed, relative to the amount of reduced hemoglobin present, by administration of testosterone.[53] Androgen, as well as progesterone, has been observed to decrease the excitability of the peripheral blood vessels in the skin of normal, castrated and eunuchoid men, while estradiol was observed to have only a transitory and slight effect in this respect.[54] Testosterone and estrogens were observed to cause increased plethysmographic response and to lower the threshold response of blood vessels of the skin to oxygen deprivation, which would have significant metabolic effects.[54] Administration of estrogen was followed by decrease in capillary pressure.[55]

The high levels of urinary creatine in the photosensitive patients during the active phases of the eruptions may or may not be significantly related to protein metabolism in the skin. Studies of this phase of the problem are now in progress.

## SUMMARY AND CONCLUSIONS

Significant clinical improvement has been effected in 4 cases of dermatomyositis by the injection of testosterone propionate. Clinical improvement was accompanied with significantly increased ability to retain exogenous creatine, increased muscular strength and moderation of cutaneous lesions. Amino acid and vitamin therapy has been observed to be of value in mediating the response to steroid therapy in these cases. The degree of clinical improvement was observed to be determined by the duration of the disease. It is imperative that the

52. Edwards, E. A.; Hamilton, J. B.; Duntley, S. C., and Hubert, G.: Cutaneous Vascular and Pigmentary Changes in Castrate and Eunuchoid Men, Endocrinology **28**:119, 1941.

53. Reynolds, S. R. M.; di Palma, J.; Hubert, G., and Foster, I.: Dermovascular Actions of Certain Steroid Hormones in Castrate, Eunuchoid and Normal Men, J. Clin. Endocrinol. **2**:228, 1942.

54. Reynolds, S. R. M., and Foster, I.: Peripheral Vascular Action of Estrogen in the Human Male, J. Clin. Investigation **18**:649, 1939.

55. Carloni, E.: L'azione degli estratti ovarici sull'atteggiamento dei capillari e sulla loro pressione, nelle varie fasi de la rivoluzione funzionale utero ovarica, Arch. di ostet. e ginec. **17**:327, 1930.

diagnosis be made early, before permanent changes in the vascular structures have been produced and widespread muscular destruction has occurred.

Evidence of disturbed ovarian function was observed in 13 female patients with lupus erythematosus. There was moderate to severe creatinuria during active stages of the diseases and comparatively low 17-ketosteroid excretion. Seven patients received steroid hormones, with beneficial results. One patient with chronic discoid lupus erythematosus was relieved of premenstrual exacerbations.

Six men with polymorphic photosensitive eruptions presented moderately depressed or low 17-ketosteroid excretion accompanied with creatinuria during active stages of the eruption.

Minimal doses of estrone ("theelin") effected cures in 2 cases of hydroa vacciniforme in young girls. One 18 year old youth with seminal insufficiency was treated with pregnant mare's serum.

It is suggested that in the group of diseases presented there is evidence of disturbed steroid and protein metabolism, as evidenced by abnormal creatinine-creatine and 17-ketosteroid excretion.

## ABSTRACT OF DISCUSSION

DR. MAURICE J. REUTER, Milwaukee: We are indebted to Dr. Lamb for bringing to our attention these studies on dermatomyositis, lupus erythematosus and polymorphic photosensitive eruption.

The most intriguing part of this presentation is the fact that he has utilized a new endocrinologic method of investigation, the chemical determination of the urinary 17-ketosteroids, in the study of these three conditions.

The urinary 17-ketosteroids are end products of androgen metabolism and apparently are derived from two glands of internal secretion. The adrenal cortex is the primary source, and a small amount is derived from the testes. Little is excreted in childhood, but with the onset of puberty there is a decided increase in the male and also in the female subjects. The daily excretion is fairly constant for each person.

Increased urinary 17-ketosteroid excretion is of diagnostic significance in adrenal cortical tumors and functional interstitial cell tumors of the testes and probably results from the excessive production of androgen by these tumors.

The significance of reduced excretion of 17-ketosteroids is not well understood. The excretion is decreased in Addison's disease and in castrated male subjects because of decreased production; it is reduced in a variety of diseases of the liver, presumably as a result of failure of hepatic function necessary in intermediary metabolism.

However, it is also reduced in a variety of unrelated conditions, such as malnutrition, chronic sepsis, carcinomatosis, ulcerative colitis, rheumatoid arthritis, diabetes, anemia, hyperthyroidism and hypothroidism. The significance of this reduced urinary 17-ketosteroid excretion in these conditions will not become apparent until a great deal more becomes known concerning their metabolism. This must make one cautious in attaching too great significance to the occurrence of decreased 17-ketosteroid excretion in any single clinical condition.

The second point of interest in this paper lies in the reemphasis on the creatinuria that occurs in dermatomyositis and in the demonstration of similar creatinuria in lupus erythematosus and polymorphic photosensitive eruption.

Some degree of creatinuria is normally present in children and frequently in women. Pathologically it occurs in wasting diseases and is a prominent observation in muscular dystrophies and thyrotoxicosis. Unfortunately, as with the 17-ketosteroids, knowledge of the metabolism of creatine is incomplete.

Creatinuria can sometimes be favorably influenced by the administration of testosterone. Positive nitrogen balance and gain in weight result from this form of treatment.

Dr. Lamb's studies have shown low normal 17-ketosteroid excretion and creatinuria in these dermatologic conditions, and his patients have apparently benefited from treatment with testosterone. These facts fit in with the incomplete knowledge of androgen and creatine metabolism. An analogous condition exists in thyrotoxicosis; similar creatinuria and low normal 17-ketosteroid excretion in this condition have led several investigators to utilize testosterone, with similarly beneficial results.

In view of the diversity of clinical conditions presenting these same observations, however, it appears that the beneficial effects obtained by Dr. Lamb are nonspecific in nature. Nevertheless, this form of treatment may prove to be an adjunct in the treatment of these diseases, and it is to be hoped that his good results can be confirmed in a larger series of cases.

DR. JOHN H. LAMB: It will take many more cases and years of carefully made endocrinologic studies before any final conclusions can be drawn.

For example, in lupus erythematosus in female subjects, studies of vaginal smears at definite intervals in the cycle and an endometrial biopsy on the first day of menstruation will probably tell more of the estrogen-androgen function than urinary 17-ketosteroid determinations.

My co-workers and I have received an adequate grant for 1947-1948 by the National Research Council. We have a great deal to learn and hope to give more in detail of several of these problems at a future date.

# SPOT TEST FOR SYPHILIS

## Using the Modified Meinicke Antigen of Ford Robertson and Colquhoun

R. F. LANE, F.I.M.L.T.
SHENLEY, HERTS, ENGLAND

THE MEINICKE *Klaerung* (clarification) test for syphilis is better known in the hospitals for mental diseases than in the general hospitals in England. Geographically, it is better known and more widely used on the European continent than in North and South America, where the precipitation tests of the Kahn type and their numerous modifications have received greater attention.

For some time after its inception, the Meinicke test was treated with suspicion, on the grounds of nonspecificity. It was claimed that reaction took place with some tropical diseases, notably malaria, and with some febrile conditions, especially tuberculosis. But the Wassermann test is not entirely specific, and positive results are sometimes elicited in the absence of syphilis in such conditions as pregnancy, malaria and infectious mononucleosis, while common experience shows that 1 to 2 per cent of serums give a positive Wassermann reaction (although perhaps only weakly), which may be due to the temporary appearance of some anticomplementary substance in the blood which has usually disappeared when the test is repeated at a later date.

The Wassermann reaction, however, is still taken as the hypothetic criterion of accuracy, and results of other tests for syphilis are usually compared with it. In this present work a Meinicke spot test has been made in parallel with the standard Meinicke technic and the Wassermann test, and the results from all three tests are compared and discussed.

The advantage of all precipitation tests is that they can be performed at any time and on any number of specimens, while, because of such factors as the preliminary preparatory work and complement titration, it is hardly worth while to perform the Wassermann test on a small number of specimens.

The Meinicke test is a colloidal test which employs a cardiac extract plus tolu balsam as the antigen. Solutions of sodium chloride

From the Pathological Laboratory, Shenley Hospital, Shenley, Herts, England.

constitute the electrolyte, and the prepared antigen has a milky opaque appearance. Precipitation of the colloids takes place when the antigen is brought into contact with a syphilitic serum or cerebrospinal fluid, and clarification takes place because of sedimentation of the precipitated colloids. A normal serum or cerebrospinal fluid has no effect on the colloidal state, and the mixture remains milky and opaque.

One possible disadvantage of the Meinicke test is the time lag necessary for the full degree of sedimentation of the precipitated colloid. It is usual to allow an optimum time of eighteen hours after the mixing of the serum and the antigen before the reading. The spot test is free from this disadvantage in that this reaction time is reduced to ten minutes.

The original antigen (Adler-Apotheke, Hagen) was formerly used in this laboratory, but for some years past my co-workers and I have been using the modified antigen of Ford Robertson and Colquhoun (from the Neuro-Psychiatric Research Institute, Shelley Road, Glasgow, Scotland).

## METHOD

*Parallel Tests.*—The Wassermann and standard Meinicke tests were used in parallel with the spot test.

1. *Wassermann Test:* The no. 1 method of the Medical Research Council (Wyler 1929[1]) has been employed throughout the series, with three times the minimum hemolytic dose of complement as control and three and five times the minimum hemolytic dose of complement for the test. The unit volume for reagents was 0.1 cc.

2. *Meinicke Test* (Ford Robertson—Colquhoun Modification): The Reagents used in the Meinicke test were (*a*) 3 per cent, 1.5 per cent and 1 per cent aqueous solutions of sodium chloride, (*b*) stock antigen and (*c*) the patient's serum (not inactivated) or cerebrospinal fluid.

*Preparation of the Sensitized Antigen.*—Into each of three test tubes are placed 9 parts of 3 per cent, 1.5 per cent and 1 per cent solutions of sodium chloride, respectively. Into each of three other test tubes is placed 1 part of stock antigen. The three tubes with the solution of sodium chloride are then placed in a water bath at 56 C., and when the temperature of the solution reaches that of the surrounding water, the tubes of antigen are placed in the bath for two minutes. At the end of this period, the contents are mixed by pouring rapidly from one tube into the other six times (one tube of solution of sodium chloride and one tube of antigen) so that the final result is three tubes of sensitized antigen containing 3 per cent, 1.5 per cent and 1 per cent solution of sodium chloride, respectively. The antigen is now ready for use and *must* be used immediately.

*Test Proper.*—Into three test tubes are placed 0.3, 0.2 and 0.1 cc., respectively, of serum or cerebrospinal fluid. To the first tube (0.3 cc.) is added 0.5 cc. of

1. Wyler, E. J.: The Wassermann Test: Technical Details of no. 1 Method M.R.C. (Modified), Medical Research Council, Special Report Series, no. 129, London, His Majesty's Stationery Office, 1929.

antigen containing 3 per cent solution of sodium chloride; to the second tube is added 0.5 cc. of antigen containing 1.5 per cent solution of sodium chloride, and to the third tube is added 0.5 cc. of antigen containing 1 per cent solution of sodium chloride. All tubes are then thoroughly agitated and allowed to stand for an optimum time of eighteen hours before reading.

Reading: The strength of a positive reaction is estimated by the degree and extent of the clarification. The strongest reaction takes place with the smallest amount of of serum (0.1 cc.), and the results are expressed on this basis as shown in table 1.

The "doubtful" Meinicke reaction is nearly always reckoned as negative and is certainly not called positive unless the result is confirmed by a parallel test (Ford Robertson and Colquhoun[2] and Thomas and Ford Robertson[3]).

*Meinicke Spot Test.*—With the standard Meinicke test, reaction takes place when the warm antigen is added to the material being tested, but eighteen hours must elapse to allow the colloid to settle to the bottom of the tube, with the resultant clarification of the upper layer. In the spot test an attempt has been made to cut down the time factor by prolonging the reaction temperature, by

TABLE 1—*Results of Tests with Varying Amounts of Serum*

| Case No. | Amount of Serum | | | Result |
|---|---|---|---|---|
| | 0.3 Cc. | 0.2 Cc. | 0.1 Cc. | |
| 1 | —<br>or —<br>or + | —<br>+<br>+ | +<br>+<br>+ | Strongly positive |
| 2 | + | + | ± or — | Moderately strong positive |
| 3 | + | + or ± | — | Positive |
| 4 | + | ± or — | — | Weakly positive |
| 5 | ± | — | — | Doubtful |
| 6 | — | — | — | Negative |

employing a mechanical means of establishing the presence of the precipitation and by increasing the concentration of serum.

As a preliminary step, a slide containing three wells was used, and 1 drop of serum was placed in each well and then 1 drop of each antigen and solution of sodium chloride mixture. The contents of the three wells were then stirred with a glass rod, and the slide was placed in an incubator at 56 C. (a paraffin-embedding oven is suitable) for ten minutes, after which it was removed and rocked with a rotatory motion for one minute. A positive reaction of a specimen of serum or cerebrospinal fluid is indicated by immediate precipitation, producing a fine granularity. With continued rocking there is a tendency toward "agglutination" of the precipitated material, giving the appearance of large and small granules in a relatively clear fluid.

The time of ten minutes is the most convenient, yielding the maximum effect without evidence of drying. Fifteen minutes at this temperature results in almost completely drying of the contents of the well. The temperature of 56 C. is selected, as this is the temperature at which the antigen and the solution of sodium chloride are mixed. The reaction also takes place at 37 C., but the time required to

2. Ford Robertson, W. M., and Colquhoun, D. B.: J. Ment. Sc. **85**:584, 1939.
3. Thomas, J. C., and Ford Robertson, W. M.: J. Ment. Sc. **85**:1241, 1939.

produce a comparable result is between twenty and thirty minutes and there is a greater tendency toward drying before the maximum reaction is seen.

With the specimens of serums used it was noticed that no matter where reaction took place with the tube method, it was always evident in the well in which 3 per cent solution of sodium chloride had been added. Following confirmation of this, it was decided to dispense with three antigen mixtures and use only the antigen mixture containing 3 per cent solution of sodium chloride.

Final Technic: The final technic involves the following steps:

1. Into a test tube are placed 9 parts of 3 per cent solution of sodium chloride, which is permitted to stand in a water bath at 56 C.

2. Into a second tube is placed 1 part of antigen. When the temperature of the solution reaches 56 C. the tube of antigen is placed in the water bath for two minutes.

3. The contents of the tubes are mixed by pouring rapidly from one into the other six times.

4. Into the well of a slide is placed 1 drop of serum and then 1 drop of the sensitized antigen; a glass rod is used for stirring, and the slide is placed in an incubator at 56 C. for ten minutes.

5. The slide is then removed and rocked with a rotatory motion for one minute.

It is important that the sensitized antigen be used immediately.

Reading: Results are interpreted as follows:

1. Decided precipitation and agglutination indicate a positive reaction.
2. Fine granularity confirmed microscopically indicates a doubtful reaction.
3. No change macroscopically or microscopically indicates a negative reaction.

An estimation of the strength of the positive reaction is possible, based on the rapidity with which the reaction becomes evident and the size of the agglutinated particles.

The technic as outlined has been used for the results to be described.

*Material Examined.*—The material examined consisted mainly of specimens of serum submitted for Wassermann and Meinicke tests, these tests being part of the routine examination carried out for all patients admitted to Shenley Hospital. Specimens of serum were also received from a military hospital, including specimens sent for the determination of the presence or absence of syphilis and a number from patients known to have syphilis, taken during and after treatment. Specimens of serum were also received from other hospitals, making a total, including control specimens from persons with infectious and febrile conditions, of 858 specimens of serum. The same routine was used for 142 specimens of cerebrospinal fluid, making a total of 1,000 specimens tested. Each specimen of serum and cerebrospinal fluid had all three tests (Wassermann, Meinicke standard and Meinicke spot test) performed on it.

## RESULTS

The results have been classified under three headings:

1. Positive results—a definite positive reaction to the individual tests.
2. Doubtful results
   (*a*) A "doubtful" Wassermann reaction is the interpretation given to incomplete fixation of three times the minimum hemolytic dose of complement.

(*b*) A "doubtful" Meinicke reaction is the reading given when "partial clarification without sedimentation is observed in one tube only." This usually takes place in the tube containing 0.3 cc. of serum.

(*c*) A "doubtful" reaction to a spot test is one in which "slight granularity is observed and which is confirmed microscopically."

Among the 48 instances of disagreement were 25 specimens of serum from patients who were known to have syphilis and who had undergone or were undergoing treatment. If these are omitted the

TABLE 2.—*Results Obtained in All Three Tests of Serum*

| Results | No. of Specimen |
|---|---|
| Negative agreement (negative reaction to all three tests) | 721 |
| Positive agreement (positive reaction to all three tests) | 62 |
| Disagreement | 48 |
| Total | 831 |

TABLE 3.—*Disagreement in the Results of the Three Tests of Serum in 23 Cases*

| No. of Cases | Clinical Diagnosis | Reaction to Spot Test | Meinicke Klaerung Reaction | Wassermann Reaction |
|---|---|---|---|---|
| 1 | Dementia paralytica | + | − | − |
| 2 | a) Conflicting Wassermann reaction<br>b) Dementia paralytica | ±<br>± | −<br>− | ±<br>± |
| 4 | Clinical syphilis | − | + | + |
| 3 | a) Dementia paralytica<br>b) Nothing known<br>c) Conflicting reports* | −<br>−<br>− | −<br>−<br>− | ±<br>±<br>± |
| 1 | Suspected syphilis | ± | − | ± |
| 2 | a) Elephantiasis<br>b) Nothing known | −<br>− | ±<br>± | ±<br>± |
| 10 | Including 3 cases of suspected syphilis, the remainder being of varied clinical pictures | − | − | ± |

*This patient had a schizoid personality. He was in his early twenties and had seen service in the tropics. Previous examinations had yielded a persistently negative Kahn reaction, but on admission he was observed to have a positive Wassermann reaction. It remained positive over a period in which the test was repeated three times and became negative after antisyphilitic treatment.

cases in which there was disagreement are reduced to 23 in a total of 806. Details of the 23 cases are shown in table 3.

The Wassermann reaction was positive for 9 patients, all of whom had syphilis. For 4 of these patients the standard Meinicke reaction agreed with the Wassermann reaction; for 2 the reaction to the spot tested agreed with the Wassermann reaction, and for 3 the Wassermann reaction alone was positive. In 1 case the spot test alone yielded a positive result in the presence of syphilis.

Tests in the remaining 13 cases in table 3 yielded "doubtful" results. One doubtful reaction to a spot test and to a Wassermann test

in a case of suspected syphilis was probably indicative of a true diagnosis, while the 2 instances in which the standard Meinicke and Wassermann tests gave doubtful resuts were not clinically suggestive of syphilis and the results were probably false. Tests in the case of elephantiasis were recently repeated, and reactions were observed to be completely negative.

Among the 10 cases in which only a doubtful Wasserman reaction was elicited, there were 3 cases of suspected syphilis, 1 each of vaginitis and claudication and 5 cases in which nothing was known, but repeated tests in 2 cases elicited negative results. Generally one observes that 1 to 2 per cent of the specimens of serum give this doubtful Wassermann reaction, and in all probability the 10 cases mentioned here constitute the usual number of such results in the examination of 831 specimens.

Omitting the reactions in the 25 cases of known syphilis during or after treatment, the results showed that the reaction to the standard Meinicke test agreed with the Wassermann reaction in examinations

TABLE 4.—*Results in Cases of Known Syphilis During or After Treatment*

| No. of Cases | Reaction to Spot Test | Meinicke Klaerung Reaction | Wassermann Reaction |
|---|---|---|---|
| 11 | + | + | — |
| 4 | + | — | — |
| 2 | ± | ± | — |
| 4 | ± | — | — |
| 1 | ± | — | ± |
| 3 | — | — | ± |

of 790 out of 806 specimens, an over-all agreement of 98 per cent. The reaction to the Meinicke spot test agreed with the Wassermann reaction in examinations of 786 specimens, giving a percentage of agreement of 97.5 per cent. It is interesting to note that in no case did the spot test elicit a positive result in the absence of syphilis, a fact which suggests that the antigen possesses a high degree of specificity.

In only 4 cases did the Wassermann test elicit a positive reaction, as against 13 cases in which the reaction to the routine Meinicke test still remained positive and 22 cases in which the reaction to the spot test was still positive. These results support the opinion that the Meinicke reaction remains positive for some time after the Wassermann reaction becomes negative (Thomas[3] and Colquhoun and his collaborators[4]).

4. Colquhoun, D. B.; Kyles, W. B., and Rannie, I.: J. Path. & Bact. **57**:249, 1945.

The altered technic for the spot test tended to amplify this phenomenon. Instances have been reported in which the Meinicke reaction has become "fast," but this applies to other tests besides the Meinicke test; indeed, Wassermann-"fast" serums have been reported.

Both instances of disagreement were in patients suffering from clinical dementia paralytica. In 1 case the reactions to both the spot test and the standard Meinicke test were positive, with a negative Wassermann reaction. This is not an infrequent observation in cases of dementia paralytica. In the second case there were positive reactions to routine Meinicke and Wassermann tests, with a negative reaction to the spot test. One possible reason for the discrepancy may have been that the antigen normally used for serum is not considered

TABLE 5.—*Analysis of Results Obtained Using All Three Tests on Cerebrospinal Fluid*

| | |
|---|---|
| Negative agreement (reactions to all three tests negative) | 130 |
| Positive agreement (reactions to all three tests positive) | 10 |
| Disagreement | 2 |
| Total | 142 |

TABLE 6.—*Results Obtained from Control Specimens of Serum of Patients with Varying Clinical Pictures of Active Febrile and Infectious Conditions*

| Clinical Condition | No. of Cases | Reaction to Spot Test | Meinicke Klaerung Reaction | Wassermann Reaction |
|---|---|---|---|---|
| Active tuberculosis | 21 | — | — | — |
| Malaria | 1 | — | ± | — |
| Infectious mononucleosis | 2 | — | — | — |
| Brucellosis | 1 | — | — | — |
| Pyrexia with adenitis | 1 | — | — | — |
| Kala=azar | 1 | — | — | A.C.* |

*Although this serum was fresh the Wassermann test elicited an anticomplementary result.

wholly suitable for cerebrospinal fluid. The rapid change in the pH of cerebrospinal fluid on standing, due to the liberation of carbon dioxide, affects the balance of the antigen, and with old fluid the results may occasionally be unreliable. With cerebrospinal fluid, as with blood, there have been no instances of false positive reactions with the spot test, in spite of the speeding up and the increase in sensitivity.

It is interesting to note that in the case of malaria a doubtful Meinicke result was elicited, while the reaction of the spot test remained negative. Bearing in mind the fact that this type of Meinicke result should be called negative unless confirmed by other tests, one would be justified in calling this a negative result.

In the relatively small number of control specimens of serum, there is nothing to support the suspicion that the Meinicke test may

elicit false positive reactions with active tuberculosis or other pyrexial conditions.

SUMMARY

A rapid method for the diagnosis of syphillis by serologic reaction is described. The method employs the standard Meinicke (Ford Robertson-Colquhoun modification) antigen.

It has been used in parallel with the standard Meinicke technic and the Wassermann test in 858 specimens of serum and 142 of cerebrospinal fluid.

The results with the rapid method (spot test) were shown to be in agreement with the Wassermann reaction in 97.5 per cent of the tests, while the results with the standard Meinicke test were in agreement with the Wassermann reactions in 98 per cent of cases.

The reaction to the routine Meinicke test tends to remain positive after the Wassermann reaction has become negative, and the reaction to the spot test also has this tendency.

The results obtained from tests of cerebrospinal fluid are comparable with those for blood, but the small amount of material (142 specimens of fluid) does not lend itself to definite conclusions.

Dr. O. Fitzgerald, Medical Superintendent of Shenley Hospital, gave encouragement and permission to publish the results obtained.

Mr. G. Usher of Clare Hall Hospital, Mr. Hester of Napsbury Hospital and my colleagues in the pathologic laboratory of a military hospital supplied many of the specimens of serum tested.

# TREATMENT OF LOCALIZED SCLERODERMA (MORPHEA) WITH BISMUTH COMPOUND

JAMES M. FLOOD, M.D.
SAYRE, PA.
AND
JOHN H. STOKES, M.D.
PHILADELPHIA

IN 1937 two articles appeared in the French literature dealing with the successful treatment of localized scleroderma (morphea) with bismuth compounds. Weissenbach, Lévy-Franckel and Martineau[1] reported improvement in 1 case after the use of sodium bismuth iodide. Sézary[2] had encouraging results in 2 patients treated with bismuth hydroxide in oil ("muthanol").

After the successful treatment in 2 cases of localized scleroderma, one of us (JHS) suggested the use of bismuth compound in a case presented at the meeting of the Philadelphia Dermatological Society on Dec. 20, 1940.[3] Anderson,[4] following Stokes's suggestion, reported 75 per cent improvement in a girl aged 12, suffering from linear scleroderma of nine years' duration, after twelve injections of bismuth subsalicylate (0.13 Gm. each). Since these preliminary reports, McGuire,[5] Smith,[6], Rothman,[7] Anderson,[8] Stokes,[9] Klauder,[10] Counter[11]

---

From the Section of Dermatology and Syphilology, Guthrie Clinic, Sayre, Pa., and the Graduate School of Medicine, University of Pennsylvania, Philadelphia.

1. Weissenbach, R. J.: Lévy-Franckel, A., and Martineau, J.: Sclérodermie en plaques améliorée par la traitement bismuthisque, Bull. franc. de dermat. et syph. **44**:1838 (Nov.) 1937.

2. Sézary, M. A.: Le traitement de la morphée en gouttes (white spot disease) par les injections bismuthiques, Bull. Soc. franc. de dermat. et syph. **44**:1981 (Dec.) 1937.

3. Stokes, J. H., in discussion on Thomas, C. C.: Calcinosis and Scleroderma, Arch. Dermat. & Syph. **44**:125 (July) 1941.

4. Anderson, N. J.: Linear Scleroderma, Arch. Dermat. & Syph. **45**:1217 (June) 1942.

5. McGuire, J., in discussion on Garner, V. C.: Morphea, Arch. Dermat. & Syph. **49**:384 (May) 1944.

6. Smith, E. M., Jr.: Circumscribed Scleroderma (Morphea), Arch. Dermat. & Syph. **50**:424 (Dec.) 1944.

7. Rothman, S.: Circumscribed Scleroderma, Arch. Dermat. & Syph. **51**:77 (Jan.) 1945.

and Anderson[12] have suggested its use or added further reports of the use of bismuth compound in the treatment of localized scleroderma.

Seven patients with localized scleroderma have been treated by us, with encouraging results. Bismuth hydroxide ("muthanol") and solution of sodium bismuth iodide and sodium iodide in propylene glycol containing saligenin and acetic acid ("iodobismitol") were used, but according to other reports bismuth subsalicylate is also effective.

## REPORT OF CASES

CASE 1.—R. L., a white girl, was first seen in January 1933, at the age of 3 years. At that time she had a large triangularly shaped lesion in the left upper quadrant of the abdomen. The cutaneous surface appeared thin and atrophic, and the lesion was firm and of a deep doughy nature. In addition to this lesion there were patches of dry scaly atrophic skin in both anterior axillary folds, over the right breast and on the right buttock. Numerous telangiectases were noted throughout the atrophic patches, but these patches lacked the doughy consistency of the other lesions. A diagnosis of localized scleroderma was made, and the child was given tincture of belladonna, whole pituitary, thyroid and suprarenal. Locally the lesions were rubbed with compound ointment of menthol, followed by ultraviolet irradiation. In spite of this treatment sclerodermatous lesions continued to develop in the patch that previously showed only atrophy.

She was not seen again until April 1942, at which time she was 12 years of age. Her mother stated that the lesions had remained approximately the same as they were in 1933 until recently, when she noted some new lesions about the upper portion of the abdomen. On April 3, treatment with a sodium bismuth iodide and sodium iodide preparation was begun, and she received 1 cc. intramuscularly twice weekly for nine injections, then 2 cc. twice weekly for eight injections (total seventeen injections). It was noted after the sixth injection that the more recent adbominal lesions were less infiltrated and had begun to scale on the surface. By May another lesion appeared to be softer. During the summer, while the patient was at a summer camp, treatment was discontinued. She was again seen in October, at which time it was noted that there had been decided improvement in all of the lesions. A letter from the patient's mother in March 1946 indicated that there had been no further improvement, and no further treatment has been given.

CASE 2.—B. P., a white girl, noted a small white patch on her chin about the size of the end of her little finger in January 1936, at the age of 16. It gradually became larger and extended downward over the neck. With this progression, she noted slight stiffness of the skin and had some difficulty turning her head. During

8. Anderson, N. P., in discussion on Counter, C. E.: Localized Scleroderma, Arch. Dermat. & Syph. **51**:286 (April) 1945.

9. Stokes, J. H., in discussion on Beerman, H., and Morgan, H.: Morphea-Like Scleroderma, Arch. Dermat. & Syph. **53**:65 (Jan.) 1946.

10. Klauder, J. V.: Morphea, Improved by Bismuth Therapy, Arch. Dermat. & Syph. **53**:392 (April) 1946.

11. Counter, C. E.: Localized Scleroderma: Result of Bismuth Therapy, Arch. Dermat. & Syph. **53**:432 (April) 1946.

12. Anderson, N. P., in discussion on Wakefield, R. F.: A Case for Diagnosis (Localized Scleroderma), Arch. Dermat. & Syph. **53**:537 (May) 1946.

1937 a number of other lesions appeared simultaneously on the right cheek, right hand and her back. She was first seen by one of us (JHS) in July 1938. At that time there was slight edema of the dorsa of the hands, with definite limitation of upward and backward movement of the hand. She had an extensive macular and confluent "white spot disease" over the nape, extending down the neck and over the shoulders, with similar lesions in the antecubital spaces. Larger and more heavily infiltrated plaques were present on the chin and anterior aspect of the neck, with some "hide binding." There were no violaceous borders about any of the lesions.

Previous treatment had consisted of ultraviolet irradiation and ammonium chloride and calcium given internally, with no improvement. A diagnosis of morphea-like scleroderma was made. It was recommended that treatment with ammonium chloride be continued and that treatment with acetyl-beta-methylcholine chloride by iontophoresis be instituted.

She returned for observation in July 1939, after having followed previously outlined treatment for the better part of a year. It was felt that she had shown 40 per cent improvement, and no new lesions had appeared. It was then suggested that she be given bismuth compound, and 80 to 100 mg. of bismuth in the form of bismuth hydroxide (1 cc. of "muthanol") was given intramuscularly. All other treatment was discontinued, and the patient was given fifteen additional injections of the bismuth hydroxide preparation (2 cc. of "muthanol" once a week). At the end of the course there had been definite further improvement. A second course of fifteen injections was given after a three-months' rest period. She was seen in June 1940, one month after the conclusion of the second course of treatment with bismuth hydroxide, and it was felt that improvement could be rated at 99 per cent. She was given a third course, of twelve injections, and in December 1940 her physician stated the belief that she was completely well. She was seen again on July 14, 1942, and showed no active sclerodermatous lesions, and except for the atrophic remains her skin was completely clear. In April 1945, there was no evidence of recurrence, but on May 22, 1946, she reported that a new lesion had appeared between the scapulas. It measured 5.5 by 2.5 cm.

CASE 3.—M. A., a white woman aged 32, had been under our care for discoid lupus erythematosus of the face since August 1935. In June 1939, at the age of 32, a large plaquelike lesion developed on the anterior aspect of the left thigh, extending from the crest of the ilium to the knee. This plaque consisted of numerous morpheiform lesions with retiform pigmentation. She was advised to return for treatment with a bismuth preparation, but did not report until December 1941. From December 30 to May 29, 1942 she received 2 cc. of a sodium bismuth iodide and sodium iodide preparation twice weekly. In June 1942, it was noticed that the lesions had improved about 75 per cent.

CASE 4.—W. S. was a white woman, aged 58. In March 1939, a firm smooth lesion developed on the left side of the neck, just above the supraclavicular area. Eight months later, a similar lesion appeared on the middle portion of the extensor surface of the left forearm. The plaques measured 6 by 2 cm. and 8 by 2 cm., respectively, and were firm and of a lardaceous nature. A diagnosis of localized scleroderma was made, and the patient was given thirty injections of bismuth hydroxide in oil, 2 cc. once weekly. She was seen again in March 1941, at which time the plaque on the arm had almost completely disappeared and the one on the neck was 50 per cent improved. A letter received from her son in 1943 indicated that the lesion had disappeared from her arm and that there was only a little thickening of the plaque on her neck.

CASE 5.—R. H., a white woman aged 22, in January 1941, while bathing, noted a hard "knot" in the skin of the left breast. She consulted her physician in March.

She was first seen by us on March 25, at which time she presented an irregularly shaped firm plaque on the upper portion of the left breast. It was about 3 cm. in diameter and was slightly reddish blue. There was no violaceous border. The plaque was freely movable and was not attached to the underlying tissue of the breast. The nipple was normal, and the axillary lymph nodes were not enlarged. A biopsy was made, and the histologic observations were compatible with scleroderma.

She was given a course of ten injections of a sodium bismuth iodide and sodium iodide solution, and there was gradual improvement in the lesion. A follow-up letter from the patient in November 1946 indicated that the lesion had completely disappeared and there had been no recurrence or new lesions.

CASE 6.—B. D., a white woman, noted the development of typical lesions of morphea guttata in April 1941. The process was located on the arms, legs, right shoulder and adjacent region of the back and on the lower portion of the abdomen. She was advised to take injections of a solution of sodium bismuth iodide and sodium iodide, 2 cc. every five days. She was seen again after the seventh injection, and there had been remarkable improvement in all of the lesions. All of them had become soft and pliable, and others had disappeared completely. She reported after completing the first course of twenty injections, and at that time the old patches had all shown improvement but several new patches had appeared on the arms. A rest period of two months was advised, and then a second course of treatment was given, 2 cc. of the same preparation once a week. In February 1943 treatment was changed to bismuth hydroxide, 1 cc. once a week (65 mg. elemental bismuth). After 14 injections were given the lesions had all undergone some involution. Another rest period was advised, during which she was to take ammonium chloride and shift her diet to the acid-ash side. In addition, ultraviolet irradiation was to be used. During this period all the lesions became more active, and on May 10 it was advised that she take 2.5 cc. of bismuth hydroxide suspension once a week. After eleven injections there had been decided improvement, rated at 75 per cent. Treatment with bismuth compound was continued until the patient had completed the course of twenty injections. In May 1944, another course of fifteen injections of the sodium bismuth iodide and sodium iodide preparation was recommended. It was also suggested that the patient take "mecholyl bromide" N. N. R. (acetyl-beta-methylcholine bromide), 200 mg. twice a day, but she was unable to do this because of vomiting even on half dosage. In October 1944, it was noted that the lesions were better and showed no activity. A letter from the patient in January 1946 indicated that there might be some activity of the lesions.

CASE. 7— I. R., a white woman aged 59, in March 1942 noted the development of several small depigmented patches on the volar surfaces of the wrists and dorsa of the hands. New patches developed, and the older ones increased in size. She had no itching or pain with these lesions. She was first seen in September. The cutaneous changes at the time of the first examination were most apparent on the volar surfaces of both wrists and dorsa of the hands. The lesions were pearly white, and there was definite evidence of atrophy. In addition, she had moderate rosacea. No specific medicament was given for the atrophic lesions. She returned in November 1943, at which time it was noted that many new lesions had developed. A large morpheic band was present in the area of the xiphoid process, extending into the inframammary creases. On one edge of this band were a number of small lichen-sclerosus-like papules. Bismuth hydroxide in oil was recommended. She received six injections, 2 cc. each, from November 17 to December 30. There was only slight improvement, and the medicament was changed to a solution of sodium bismuth iodide and sodium iodide, 2 cc. given twice weekly.

In addition, she was given acetyl-beta-methylcholine bromide, 1/6 grain three times daily and the inframammary lesions were treated with five doses of roentgen rays (94 r unfiltered, each exposure). The course of eighteen injections with the sodium bismuth and sodium iodide preparation was completed March 18, 1944, and on April 22 it was noted that all the lesions had improved 50 to 60 per cent. She continued to take acetyl-beta-methylcholine bromide. By November 1945, the large submammary band was completely gone and only a small patch remained at the xiphoid and umbilicus. She reported for examination Nov. 1, 1946, and it was noted that there had been a small island of recurrence in the band of scleroderma on the anterior aspect of the chest, but the lesions had not reappeared on the wrists. On the lower part of the back a small cluster of lesions, suggesting lichen sclerosus et atrophicus of Hallopeau, remained. Four months after the completion of another course of treatment with bismuth subsalicylate the morpheic plaques had softened, but had not disappeared. Another course of treatment with bismuth compound was advised.

*Tabulation of Data in 7 Cases of Localized Scleroderma*

| Case | Sex | Age | Degree | Treatment Other Than With Bismuth Compound | No. of Injections With Bismuth Comp. | Result |
|---|---|---|---|---|---|---|
| 1 | F | 12 | Severe | Tincture of belladonna, pituitary, thyroid, suprarenal. | 17 | Good |
| 2 | F | 17 | Severe | Acetyl-beta-methylcholine bromide by iontophoresis | 43 | Good |
| 3 | F | 32 | Moderate | None | 45 | Good |
| 4 | F | 58 | Moderate | None | 30 | Excellent |
| 5 | F | 22 | Mild | None | 10 | Excellent |
| 6 | F | 30 | Severe | None | 69 | Fair |
| 7 | F | 59 | Moderate | Roentgen rays, acteyl-beta methylcholine bromide | 24 | Good |

## COMMENT

All of our patients showed improvement after receiving bismuth compound. The mode of action of the bismuth compound is not known, but, like its action in other diseases, such as lupus erythematosus and lichen planus, there is some unknown nonspecific effect. More experience will be required to determine the most effective dosage and the length of time treatment should be continued. At present it seems advisable to give a course of treatment lasting ten to twelve weeks, repeating it two or three times if necessary. Apparently some patients will require a total of fifty to seventy-five injections of bismuth compound before satisfactory results can be obtained. If there is evidence of recurrence, treatment should be repeated.

## SUMMARY

Seven cases of localized scleroderma are presented. Results of treatment with bismuth compound were excellent in 2, good in 4 and fair in 1.

# SOME OBSCURE AND PARADOXIC PROBLEMS OF SYPHILIS

U. J. WILE, M.D.
Professor Emeritus of Dermatology and Syphilology,
ANN ARBOR, MICH.

THE PATHOLOGIC response in the visceral, central nervous and cardiovascular systems to Treponema pallidum leads to innumerable clinical phenomena, which so closely simulate other conditions that they constitute challenging problems in differential diagnosis. This fact has long been recognized by clinicians and led to Osler's famous dictum: "Know syphilis and the whole of medicine is open unto you."

Less well recognized and little recorded are the many paradoxic and unexplainable manifestations of syphilis, especially the responses of the infecting organism provoked in certain tissues, contrasted with apparent tissue immunity elsewhere.

The obscure and paradoxic character of syphilis begins immediately with the infecting organism. Belatedly discovered, after innumerable unsuccessful researches extending over twenty-five years, the nature of this organism and its life history are still unsolved problems. Such knowledge as has been gained through experimentation with animals and through culture has shed little or no light on the place of the organism in nature and its life history. Paradoxically, its structure is indistinguishable from the organism causing yaws, which is clinically similar to syphilis; more difficult to understand is its apparent identical structure with the organism found in Central and South American pinta (carate), which bears no resemblance to syphilis. Moreover, no expert is as yet sufficiently skilful to distinguish the syphilis organism from the benign nopathogenic organism of the mouth, Treponema microdentium.

Laboratory experiments, involving the use of various animals, have accomplished little to clarify the nature of the organism. On the contrary, the results have rather tended to befog the question.

---

This paper was presented as the First William Allen Pusey Memorial Lecture before the Chicago Institute of Medicine, December 1946.

Published by permission of the Chicago Institute of Medicine.

## EXPERIMENTAL SYPHILIS IN ANIMALS

The earliest researches, chiefly carried out in Germany and Austria, purported to show that practically all domesticated animals, including even the horse, could be infected with human syphilis. The error of this concept, however, was soon made evident, and it now appears that no domesticated animal can be infected with syphilis in precisely the same way that the human host is. The closest approach to human syphilis was achieved with induced infection in anthropoid apes, and even in these animals a spontaneous resolution of the disease and a modification of its course differentiate it from the disease as seen in the human host.

After many years of experimentation, infection is most readily induced in the rabbit, and in this animal it is a benign local manifestation in no way analogous to the disease in human beings, but extremely valuable as a yardstick to determine the presence of the infecting organism. During the past five years Dr. Sture Johnson and I have been investigating the behavior of the organism of syphilis in various strains of white and gray mice.

The original communications on this subject were published in German by Kolle and Schlossberger. The reports of their investigation appeared in some respects so bizarre that our first problem was to repeat their experiments. Our results generally coincided with those of the two German investigators but have differed in some important respects, so that we have carried our investigations over not only into mice but into the Egyptian hamsters. As illustrative of the unusual behavior of the organism in mice, I can give briefly the following interesting and unexplainable facts. All varieties of mice can be successfully inoculated intraperitoneally, subcutaneously and through a marsupial pouch with the various strains of rabbit-borne human syphilis. Mice so inoculated are capable of reinfecting rabbits if their brain substance, spleen, gonads and lymph glands are introduced into the rabbit testes. In no instance do the successful infective inoculums from mice show either pathologic evidence of the disease, nor have any organisms ever been discernible by dark field examination of the inoculated material. The ability of the mouse to convey back to rabbits a syphilitic infection can be carried over from mouse to mouse without limitation, over many generations. Such animals carry the ability to reinfect rabbits throughout their lives. A second interesting paradoxic observation is that, while in the rabbit there invariably develops with the syphilis a seropositive reaction of the blood, the blood of syphilis-bearing mice is invariably seronegative. In many instances in rabbits infected from mice there developed a much higher blood titer with their infections than existed in the original rabbit strain.

It would appear from these experiments that mice carry the syphilis organism in an infravisible, or possibly granular, form. This hypothesis is an observation originally postulated by Levaditi and Lepine and their co-workers at the Pasteur Institute and the Alfred Fournier Institute in Paris. Further investigations carried on by us during the past year have shown us that mice harboring and capable of transmitting syphilis to rabbits are unable to convey this infectiousness to their offspring whether either parent or both parents are infected.

The possibility that the syphilis organism can undergo mutation to an infravisible form may be a determining factor in the unexplainable reactivation of foci after many years of latency and in the transmissibility of occult syphilis so frequently seen in conjugal infections. It is possible that such forms may be the activating factor in interstitial keratitis, essentially a syphilitic process, in which the spirochete as such has never been demonstrated.

We have carried out with precisely similar results in the hamster, the experiments made with mice.

## SYPHILIS IN HUMAN BEINGS

Turning now to the behavior of the organism of syphilis in human beings, one observes a peculiar selectivity of its affinity for certain structures and a paradoxic avoidance of others. Particularly are the endothelial lining and the musculature of blood vessels sites of election. Bony structures and the parenchyma of various organs, such as the brain, liver and testes, are frequently involved, whereas, the parenchyma of the thyroid, the pancreas, the kidney and the ovary are seldom the sites of syphilitic disease.

Structures lined by squamous epithelium also have an unexplainable and paradoxic affinity for involvement when compared with structures lined with columnar epithelium. By predilection, all squamous epithelium is predisposed to the early and the late manifestations of the disease, and it may be stated further that where squamous epithelium ends and columnar epithelium begins, syphilis ceases to appear.

Two notable exceptions to this rule occur in both the esophagus and the anterior and posterior vaginal walls. In connection with the esophagus, this membrane is singularly free from all but the rarest types of syphilitic lesions. Paradoxically, the adjacent squamous epithelium of the pharynx is a site of election. In contrast to the freedom of the vaginal walls from syphilitic lesions, the epithelium of the cervix and that of the vulva are, paradoxically, special sites of election.

In the cases of both the esophagus and the vaginal walls, it is to be noted that their epithelial surfaces under normal conditions do not

cornify. The reaction of the vaginal secretions may conceivably be a further inhibitive factor in the freedom of these tissues from involvement.

The reproductive organs of both sexes present a curious paradox of involvement. The testes, places of election for the production of experimental syphilis, are frequently elective sites in the acquired infection, both in the form of active syphilomas and of destruction of the seminiferous tubules, a frequent postmortem observation in old cases of syphilis. Conversely, syphilis of the ovaries is a nonexistent clinical entity and is rarely, if ever, reported pathologically. This fact becomes more curious when one considers that the child with congenital syphilis derives its infection from the mother. Attention at this point may now be directed toward the paradoxic influence of syphilis in pregnancy. Generally speaking, infection of any kind during gravidity is viewed with alarm, especially as it concerns the health of the mother. The effect of syphilis on the product of conception is definitely grave; no disease contributes more to intrauterine mortality as well as to postpartum infant morbidity than syphilis. However, in contrast to all other disease patterns, it has definitely been shown that syphilis runs a milder course in the pregnant woman than it does in the nonpregnant woman. The low incidence of serious manifestations or late sequelae in syphilis complicating pregnancy is so evident that pregnancy has facetiously been referred to as good treatment for syphilis.

Smooth muscle, particularly as it concerns the heart and all blood vessels, forms an essential part of gross and microscopic pathologic aspects of syphilis. The smooth muscle of the uterine body, however, so often the site of other pathologic changes, is never involved in either late or early syphilis. The cervix, with a squamous epithelial lining, is a site of predilection for early syphilis in direct contrast to the anterior and posterior vaginal walls, which represent squamous epithelial structures resistant to the organism.

Turning now to syphilis of the central nervous system, here again one encounters a rather extraordinary inconsistency in the reaction of comparable tissues to the invading organism. The most striking example occurs in dementia paralytica and tabes dorsalis. On the one hand, in dementia paralytica there are decided degenerative changes in the gray matter, accompanied with a rich implantation of organisms, whereas in tabes dorsalis the degenerative changes are most prominent in the white matter and entirely unaccompanied with demonstrable organisms. When these two conditions occasionally occur together, as in the tabetic form of dementia paralytica, the paradoxic reaction of the brain and cord to the infection is even more evident.

So-called asymptomatic neurosyphilis presents a picture not simulated or approached by any other neurologic disturbance. Generally speaking, the response of the delicate membranes, as well as the parenchyma itself, of the nervous system is immediately manifested by serious clinical symptoms when invasion by any micro-organism takes place, paralleling in many cases the response to actual trauma. By contrast, invasion and involvement, both early and late, of the neuroaxis by Treponema pallidum is frequently unaccompanied with any clinical symptoms and is determined solely by lumbar puncture. In early syphilis a significant degree of basilar meningitis, accompanied with pleocytosis, increase of the organic solids and positive serologic reaction, is not an infrequent occurrence without clinical symptoms.

The involvement of second and third cranial nerves in neurosyphilitic disease presents a baffling paradox. With tabes dorsalis it is rare, indeed, when there is no anisocoria. The Argyll Robertson pupil and associated optic atrophy are all too frequent concomitants of degeneration of the posterior columns. A striking contrast, the more remarkable because of proximity and active spirochetosis, is the relative infrequency with which anisocoria, the Argyll Robertson pupil and optic atrophy occur with dementia paralytica.

For many years I have been struck by habitus as an apparent influence in the determination of the type of parenchymatous neurosyphilitic disease. Observation in innumerable cases has convinced me that tabes dorsalis is more commonly seen in the asthenic type of person. Conversely, but somewhat less striking, dementia paralytica is far commoner in the pyknic types. It has not been uncommon in my experience in conjugal syphilis to see one partner with dementia paralytica and the co-partner with tabes dorsalis. To a certain degree, this fact may be related to the well known observation of psychiatrists that asthenic persons are predisposed to the schizophrenic psychoses, whereas, pyknic persons have basically cyclothymic (manic depressive) potentialities.

What has been said of the central nervous system is strikingly true also of the cardiovascular system. The resolution of all syphilitic processes, from the chancre to the gumma, results in fibrosis. These dominant changes can readily be demonstrated in the peripheral vessels in and about all syphilitic processes. Syphilis, therefore, would seem to bear some relation, in fact an important one, to the development of clinical arteriosclerosis. It may, however, be, I believe, correctly stated that, notwithstanding the predilection for vascular damage and fibrous replacement, syphilis plays an inconspicuous role in either premature arteriosclerosis or in that associated with senility.

It is a further paradoxic fact that with a decided tendency to produce macroscopic and microscopic changes at the base of the aorta,

not infrequently extending to the aortic valves, major coronary occlusion due to syphilis as a clinical or pathologic observation is rare. Of the many deaths from coronary occlusion, the fewest can be ascribed to syphilitic disease. This fact becomes more interesting when one considers that silent infarcts due to minor coronary vessel occlusions not infrequently are seen with cardiovascular syphilitic disease at autopsy.

The curious and somewhat inconsistent behavior of the syphilis organism in acquired syphilis is also reflected in congenital infections. As mentioned previously, interstitial keratitis, one of the severest manifestations of congenital syphilitic disease, is unique not only in the absence of demonstrable infecting organisms, but it is so resistant to treatment that not infrequently the unaffected eye will become involved during energetic treatment directed toward the affected one. The occasional tardy manifestations of congenital infection represent curious manifestations of the disease. It is a not infrequent happening that potential manifestations are retarded in the host with congenital syphilis until accident, other disease or, more important, pregnancy induces their appearance. It is a well known observation that the first manifestations in otherwise apparently healthy young women are interstitial keratitis and hydrops of a major joint coinciding with the onset of a first pregnancy.

Difficult to understand, also, is the not infrequent involvement of the cortex leading to definite dementia paralytica in congenital syphilis and the extreme rarity of the tabetic syndrome, in no way following the pattern of the acquired infection.

Congenital infection departs from the pattern of the acquired disease, moreover, with regard to the incidence of cardiovascular syphilitic disease. Aortic regurgitation, aortitis and aneurysm, so common in acquired syphilis, are distinct rarities either clinically or pathologically in the congenitally diseased person. The only cardiovascular abnormality is the occasional instance of congenital valvular defects, oftener diagnosed at autopsy than seen as clinical manifestations. These facts would appear to be more remarkable when one considers that the person with congenital syphilis is more thoroughly syphilized than the person with the acquired disease.

Finally, becoming more complex from year to year is the behavior of the reagents in the blood stream, originally believed to be entirely specific and now evidently not to be regarded just as any other symptom of the infection. However much one is indebted to the Wassermann and other serodiagnostic procedures for broadening the horizon of syphilis pathology, it becomes increasingly clear, as time goes on, that these reactions can in many circumstances be devoid of causative significance and, indeed, lead to misinformation

and needless therapeutic procedures. With the ever increasing sensitivity of antigenic substances, serologic methods become less informative regarding the absence or presence of syphilitic infection.

Of what significance is the reaction or test, however sensitive, which fails to reveal the disease for which it has alleged specificity until six weeks or more have passed since the host became infected? What scientific theories for specificity can account for months and years of negativity and return, with or without clinical relapse, to positivity? With positive reactions occurrng in virus pneumonia, poliomyelitis, malaria, chickenpox, leprosy, yaws and pinta, to mention several, it becomes increasingly evident that in specificity the serologic reactions to tests for syphilis, be they complement fixation or flocculation tests, lag far behind those for tuberculosis, chancroid and lymphogranuloma venereum. The increasing list of diseases which in unusual circumstances give so-called false positive reactions seems to increase with monotonous regularity, and the time has arrived when much more critical appraisal must be made in the presence of a positive reaction than appeared necessary a decade ago.

## COMMENT

The foregoing observations for the most part are not to be found in medical literature. They are impressions gained after forty years of daily contact with a disease protean in its clinical manifestations, ever devious in its pattern and unpredictable in its course. These attributes distinguish it from all other human infections. They constitute a titillating challenge to the inquiring mind. Their elucidation in some respects awaits further research into the life history of the organism. When and if this mystery is clarified, there will still remain the elusive paradoxic clinical responses to the infection the explanation of which calls for imaginative reasoning.

# GERIATRIC NUTRITIONAL ECZEMA

W. H. GUY, M.D.
F. M. JACOB, M.D.
AND
W. B. GUY, M.D.
PITTSBURGH

DURING the past several years we have studied a number of patients whose clinical and laboratory observations are grouped and presented herewith rather than details of individual cases. These patients were past middle life and presented varying degrees of edema, particularly of the aspect of the legs below the knees, usually associated with a chronic erythematous, papular, vesicular, pustular, exudative or squamous inflammatory process, of varying degrees of severity and involving the same areas. In some cases the eczematous process was much more extensive, and in a few instances chronic generalized erythroderma was present. In one of the latter, a mild diabetes was evidenced by reduced sugar tolerance. Hemostasis of varicosities or cardiac or renal disease was ruled out in all cases. Most of our patients had dental caries and/or unsatisfactory masticating surfaces. A feeling of weight and fulness with much gas after meals was frequently noted. Anorexia was usual. Constipation was a frequent, but not constant observation. The diet was unbalanced, usually being high in carbohydrates and low in proteins. Varying degrees of general debility were noted.

In nearly all cases there was relative or complete achylia. A moderate degree of hypochromatic anemia was a frequent observation. In all cases there was a diminution of the total blood protein and an alteration in the serum albumin and serum globulin ratio.

The concentration of protein in the plasma and the proportions of the fractions remain relatively constant under ordinary conditions of health.[1] While fibrinogen is essential for clotting, all three proteins serve to maintain the osmotic pressure of the blood. Protein molecules

From the Department of Dermatology, University of Pittsburgh.

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June, 1947.

1. Rowntree, L. G., and Brown, G. E.: The Volume of the Blood and Plasma in Health and Disease, Philadelphia, W. B. Saunders Company, 1929.

do not easily pass through normal capillary membranes. They exert an osmotic pressure of 25 to 30 mm. of mercury. The pressure which each fraction exerts is inversely related to the size of the molecule and directly related to its concentration in the plasma.[2] The molecular weight of serum albumin, which is in greatest concentration, is 70,000, while that of globulin is 175,000, but its concentration is considerably less. Thus, in equal concentrations serum albumin exerts an osmotic pressure two and four-tenths times that of globulin.[3] The concentration of total protein is reduced after hemorrhage, in nephritis, in malnutrition, in nutritional deficiency, during pregnancy and lactation and in parenchymatous hepatic disease.[4]

Hypoproteinemia resulting from nutritional deficiency, interference with assimilation of protein, nephritis or hepatic disease is undoubtedly the dominant factor in the production of edema.[5] The loss of serum albumin, with its relatively small molecule and greater osmotic pressure, is more important than loss of globulin. The smaller albumin molecules escape more easily. It is generally conceded that a reduction in protein to or below 5 per cent and of the albumin fraction to 2.5 per cent will result in edema.[2] We, however, have seen edema and eczema with a more moderate degree of hypoproteinemia, in which the serum albumin and serum globulin ratio was disturbed because of loss of serum albumin. Edema has been produced experimentally in dogs by placing the animals on a diet low in proteins.[6] The nutritional edema is abolished when an adequate supply of protein is given.[5] It has also been demonstrated that in a patient with nephrosis, edema can be precipitated by a diet low in proteins, when edema was previously absent. Edema may occur in patients with anemia or conditions in which the general nutrition is impaired.[7] Thus, edema is seen in beriberi, scurvy, "war edema," faulty nutrition of infants and in the geriatric state which entails such factors as poor mastication, faulty assimilation, a diet rich in carbo-

2. Best, H. C., and Taylor, N. M.: The Physiological Basis of Medical Practice, Baltimore, Williams & Wilkins Company, 1945.

3. Youmans, J. B.: The Diagnosis of Nutritional Edema with Particular Reference to the Determination of Plasma Proteins and Consideration of Their Behavior, Proceedings of the 16th Annual Conference on Nutrition and Public Health, 1938, p. 166.

4. Youmans.[3] McLester, J. I.: Borderline States of Nutritional Failure, J. A. M. A. **112**:2110 (May 29) 1939.

5. Farr, L. E., and Van Slyke, D. D.: Relation Between Protein Level and Edema in Nephrotic Children, Am. J. Dis. Child. **57**:306 (Feb.) 1939.

6. Rose, W. C.: The Significance of the Amino Acids in Canine Nutrition, Science **90**:186 (Aug. 25) 1939.

7. Castle, W. B., and Minot, G. R.: Pathologic Physiology and Clinical Description of the Anemias, New York, Oxford University Press, 1936.

hydrates, poor appetite, impaired hepatic function and general retardation and modification of metabolic processes resulting from involutional tissue changes. There is abundant evidence that with an inadequate protein reserve and edema tissues are much more susceptible to infection, pressure and mechanical or chemical irritation. Not only the eczematous reaction herewith noted but even chronic ulcerations may occur.[8]

Patients with nutritional eczema are usually amenable to a six point plan of treatment, as follows: (1) adequate mastication to be assured, (2) a diet rich in proteins, (3) administration of protein hydrolysates, concentrates and vitamins (yeast and liver fractions), (4) correction of hypochromatic anemia, (5) dilute hydrochloric acid with meals, and (6) local care in keeping with the status of the inflammatory process.

## ABSTRACT OF DISCUSSION

DR. CLYDE L. CUMMER, Cleveland: To this group, embracing the senators of dermatology, a discussion of any problem pertaining to the aging or the aged should be of immediate personal as well as professional interest.

The essayists' presentation has the virtue of brevity, more priceless because it is so rarely encountered. With masterly consciseness it constitutes an effective summary of a carefully made clinical study, which deserves further amplification because of its significance.

While dermatologists have long been alert to the cutaneous manifestations of other nutritional inadequacies, particularly those caused by vitamin deficiencies, the authors now direct attention to cutaneous changes associated with protein deficiency.

Nutritional edema is thought of as an accompaniment of war or famine. It is stated (Sebrell ) that during World War I over 22,000 cases were listed in Bohemia alone, and in the Russian famine of 1921-1922 all surviving inhabitants of certain villages were affected. We are not likely to think of the possibility of milder forms occurring in the routine of everyday civilian practice, and it is well to be on the alert. The importance of this contribution is enhanced by one's being obliged to think of the question of nutrion in elderly persons, a subject of prime importance in this day when more persons live longer and must be maintained in optimum health, not only for their own sakes but also for the benefit of the world in which they live and to which they, in turn, should still be useful.

Physiologic and biochemical considerations have been explained lucidly in the paper, in accordance with current teachings, and call for no discussion on my part.

It seems to me that from a practical standpoint the difficulty will arise in differential diagnosis in cases with clinical signs described by the authors, such as varying degrees of edema of the legs, below the knees, associated with cutaneous changes. Which of these are due to protein insufficiency and which to such conditions as varicosities and cardiac insufficiency? It is assumed that studies of the blood would be required to determine the concentration of total protein in the blood serum and the albumin-globulin ratio. However, in any event, even with mixed

8. Clements, F. W.: Diet in Relation to Tropical Ulcers, J. A. M. A. **106**:139 (Jan. 11) 1946.

causation, attention to protein insufficiency would certainly be helpful. Undoubtedly there are many elderly persons now suffering from subclinical states of protein starvation who would be benefited if all with suggestive cutaneous changes were carefully scrutinized.

Undernutrition in aged persons may result from several factors. Important among them is poor dental equipment, indequate for thorough chewing. Teeth may be carious, insufficient or even entirely missing. If there are dentures, they may be ill fitting, or use of them may cause pain. These limitations are often accepted by those so handicapped as part of the distressing process of growing old. As a result, meats are avoided and soft foods, usually of high or even concentrated carbohydrate content, are taken in preference, resulting in a shortage of protein in the diet. Frequently the appetite is impaired. It is stated that achlorhydria is the rule in about 40 per cent of persons over 60. Also, the absorptive powers and vitamin storage begin to fail with age.

In addition, certain important popular fallacies are culpable, a prominent one being that old persons should live on an abstemious diet. As Tuohy said, the "less food for old people fallacy" hinges on the supposition that for them energy for current expenditure is the chief item, and, therefore, carbohydrate and some fat with a minimum of protein should suffice. Such a diet, of course, is wholly inadequate for the continuous process of bodily repair.

Another deeply rooted fallacy is that protein causes high blood pressure. The current fad for periodic starvation has no place in the care of the aged. Tuohy emphasized also the follies of so-called "arthritic," "colitis" and other bizarre diets, shunning the use of meat, stating that physicians must teach elderly persons the importance of protein and how to get their daily quota, no matter how old they are, of 1 Gm. per kilogram of body weight. "The tea-and-toast schedule for grandma is outmoded."

I can remember, in my student days, a statement in Osler's text (which I unfortunately cannot locate now) to the effect that it would be well if aged persons were to revert gradually to the diet of their infancy, almost exclusively milk. Today one can appraise the inadequacy of such a diet, and I think that modern experts on nutrition would feel that it would be questioned merely if offered as the only source of calcium.

The regimen which has been described could doubtless be employed with benefit for all elderly persons. The emphasis should be on improvement in mastication, increase in protein and restriction of carbohydrates, on which this age group tend to lean.

We are grateful for having our interest focused on this clinical picture and for the opportunity to consider briefly the question of nutrition.

This paper complements that offered yesterday by Keim, which, together with the discussion, brought out the points that proteins are essential in tissue building and repair and that serum protein deficiencies exist in private as well as hospital patients.

I should like to ask Dr. Guy to give us some idea of the frequency of nutritional eczema in elderly persons as he observed it in his private and hospital practice, and as to whether the condition seemed to bear any relationship to the patients' economic status. Does he consider that the presence of hypoproteinemia in some of the persons not included in his study could not account for slowness of response to ordinary treatment for dematitis of the legs caused primarily by varicosities of cardiac or renal origin?

DR. GEORGE C. ANDREWS, New York: I was especially interested in the paper by Dr. Guy, because for the past ten years I have been working along similar lines.

In the last two editions of my book I mention this type of eczema, but instead of including it with "nutritional eczema," I included it with "eczema due to focal infections." This is probably an error on my part. I have thought of writing about it, because in cases in which the disease starts on the legs in middle-aged persons removal of abscessed teeth effects prompt cure.

I have not gone into the general systemic changes thoroughly, as Dr. Guy has. He has observed hypochromatic anemia and hypoproteinemia, but I have cured the patients by removal of abscessed teeth.

Just two weeks ago I saw a man from Montreal who had this same type of eczema. He had seven abscessed teeth and a white blood cell count of 17,000.

I have talked so much about focal infections that I hesitate to mention the subject, especially to my New York colleagues. There seems to be gravitation and sensitization to bacterial products from abscessed teeth. This type of disease usually starts on the legs, and then it is likely to break out on the hands and other dependent parts. Finally, it spreads and becomes universal, and, as Dr. Guy said, there is edema of the skin, usually with leukocytosis.

I am indebted to Dr. Guy for going into the matter more thoroughly than I have and observing other systemic effects to be treated accordingly. I know that in a majority of the cases cure is effected by repair or removal of the teeth, but these other methods, giving "energen foods" (purported to have a high content of protein) and protein, should be important, too.

DR. FRED M. JACOB, Pittsburgh: Dr. Andrews brought out a point which I think that Dr. Guy stressed also, and it is most important, that is, the matter of teeth.

In a previous session mention was made of the injection of plasma and various protein hydrolysates. After all, the main channel of protein is through the mouth and into the stomach, and the proper masticating surface and proper digestive juices, I think, will be of greater benefit than the injection of these materials, which is only a temporary measure, whereas the one I mentioned is permanent.

This is a fascinating subject. There are other factors that are involved. In a discussion with Dr. Martin, who is head of one of the tuberculosis hospitals, he said that when there are cutaneous manifestations in patients with tuberculosis there is a disturbance of the albumin-globulin ratio, which struck me as being interesting to dermatologists.

DR. RICHARD L. SUTTON, JR., Kansas City, Mo.: It is interesting that we all do the same thing to help aged patients, if for somewhat different reasons.

I see more nearly eye to eye with Dr. Andrews on this than with Dr. Guy, feeling that if one eliminates focal infection the disease disappears along with the hypoproteinemia and the other ailments.

That is my standard practice, and it includes not only adequate attention to the mouth—wherein the dentist's opinion is not nearly as good as my own, I say, modestly—but also includes examination of prostatic fluids and, for female patients, adequate pelvic examination and repair.

DR. WILLIAM H. GUY: Dr. Cummer asked about frequency. It is not common, of course; one sees only an occasional case.

As to diagnosis, all the aspects of unbalanced diet, with lack of mastication, the association of faulty digestion, poor appetite and assimilation and, finally, the development of edema followed by superimposed dermatitis, make the clinical picture. Demonstration of hypoproteinemia confirms the clinical diagnosis.

I agree with Dr. Andrews and with Dr. Sutton that some patients will improve with the removal of focal infection. This, in my opinion, does not happen because the focal infection is removed, but because the patient is enabled to take

care of his protein needs properly. The protein in the blood is necessarily obtained by what is put in the mouth. Over half of our patients had no teeth at all—false or natural—only a few had dental infection. Focal infection as the cause, therefore, cannot be accepted.

Hydrolsates are given until normal intake and assimilation are reestablished, and then the patient takes care of his protein needs in the proper manner and does not need supplementary feeding.

The edema, which is frequently decided, precedes the dematitis and usually disappears promptly after treatment is started. Clearing the residual dermatitis then becomes relatively easy.

# EXPERIMENTAL STUDY OF ITCH STIMULI IN ANIMALS

HANS KOENIGSTEIN, M.D.
TEL-AVIV, PALESTINE

THIS paper is a report of the use of animals for the investigation of pruritus. Except in the work of Sherrington,[1] animals have not been used hitherto for studies of pruritus. The sparsity of suitable reagents for the induction in animals of an itch paroxysm comparable to that which occurs in man partly accounts for this situation. Even Sherrington's experiments do not relate to the present study directly as they were concerned with the immediate scratch reflex of the dog to a cutaneous stimulus, whereas this work[2] deals with a sustained type of itch paroxysm which tends to fluctuate in intensity between peaks separated by periods of exhaustion.

Recent observations have made it possible to use animals for experiments with pruritus. Richet[3] obtained from the tentacles of actinia an aqueous alcohol extract which he termed thalassin. This elicits severe itching in dogs when it is administered intravenously. A treated animal scratches mainly its head, primarily with the hindlegs and secondarily also with the forelegs. Other parts of the body as well may be scratched. Occasionally the animal attempts to alleviate the persistent itching by dragging its belly on the ground, by rubbing against a wall or by rolling on its back.

Preparation of thalassin in crystalline form has not yet been achieved, and it has to be used in the form of an unpleasantly smelling gray-brown suspension. The itch effectiveness of different preparations varies. It is therefore necessary, when comparing results

---

This investigation was initiated in the Pharmacological Institute of the University of Vienna (Head of Institute, Prof. E. P. Pick) and was continued in the Department of Applied Physiology of the Hebrew University, Jerusalem (Head of Department, Prof. E. Wertheimer), with the help of a grant from the Dazian Foundation.

1. Sherrington, C. S.: Observations on the Scratch Reflex, J. Physiol. **34**:1, 1906; The Integrative Action of the Nervous System, New Haven, Conn., Yale University Press, 1920. Bruecke, T.: Tatsachen und Probleme der Physiologie nervoeser Systeme, in Handbuch der Physiologie, 1932, vol. 9.

2. Konigstein, H.: Zur Entstehung und Bekampfung des Juckreizes, Wien. klin. Wchnschr. **49**:815, 1936.

3. Richet, C.: Notizen über Thalassin, Arch. f. d. ges. Physiol. **108**:369, 1905.

obtained with different extracts, to calculate separately in each case the dose required for the production of a response of a given intensity.

When, as in the present case, an extract contains protein, anaphylactic reactions in the course of a series of injections must be expected. In the earlier part of this work I lost several animals because of shock. I was unable, nevertheless, to induce even partial immunity to the pruriginous action of thalassin in the dogs. Dogs in which an anaphylactic reaction has been induced by an injection of thalassin respond again with itching after recovery to a new injection of thalassin.

The injection of large doses of thalassin elicited side reactions, the intensity of which varied for different extracts. Among the side reactions were severe excitement, vomiting, defecation drive and drowsiness. The itch reaction was elicited only after intravenous or intracisternal injections, but not after subcutaneous or intramuscular injections, which, however, caused necroses.

The dog is an animal well suited for intravenous injections of thalassin. With this animal failure is rarely encountered, if a suitable extract is used. With other laboratory species, such as the mouse and the cat, there is response to thalassin injection with itch reactions only in a certain percentage of cases, but these animals often suffer from cramps. The disparity between the effective and the fatal dose in these animals is so small that the percentage of success in a series of experiments can be practically insignificant.

For certain purposes the method which depends on the sensitization of animals to light by means of hematoporphyrin[4] was found suitable. White mice which are exposed to a beam of intense light following treatment with hematoporphyrin show a syndrome in which uncontrollable pruritus predominates. The feasibility of this method is limited by the rarity of the photodynamic reagent.

After several series of experiments with the two aforementioned methods of inducing an itch reaction had been completed, Mehes[5] published a new procedure. This investigator injected morphine and its derivatives into the cisterna cerebellomedullaris of cats (dosage: 0.2 to 1.0 mg. per kilogram of body weight). After a brief period of quiescence, an itch reaction of mounting intensity was produced by the injection, the single region affected being the head. According to my experience the incubation period varies between two and twenty minutes. The time depends on the temperature of the in-

4. Hausmann, W.: Die sensibilisierende Wirkung des Hämatoporphyrins, Biochem. Ztschr. **30**:276, 1910-1911.

5. Mehes, J.: Experimentelle Untersuchungen über den Juckreflex am Tier, Arch. f. exper. Path. u. Pharmakol. **188**:650, 1938.

jected solution and is appreciably greater when cold solutions are injected. Otherwise similar animals can be separated into two types (one requiring a long period and the other a short period of incubation), on the basis of speed of their itch response to injection of a morphine solution.

The response takes the following form: Soon after the injection there is an intense salivary flow. Twitching of the muscles of the ear is a constant forerunner of the itch paroxysm. The paroxysm, which is relieved at intervals by brief periods of exhaustion, lasts for about one hour. In the decerebrated cat the intensity of the pruritus paroxysm is greater, and it can last more than three hours. The cat scratches mostly with the hindlegs. It bends its head against its bent paws. At the climax of the paroxysm, the head is generally held with the forelegs to keep it from slipping and the animal throws itself from side to side and rolls on its back. After forty-five minutes, as a rule, a state of excitement, a reaction which has been associated in cats with the effect of morphine, sets in and, concomitantly, the intensive itching subsides gradually. In the latent period, before an attack or in a pause, it is possible to elicit scratching by touching an external ear. Occasionally vomiting and defecation tenesmus are observed at the beginning of the attack. After termination of the attack the cats are completely normal.

The pruriginous action of morphine is not unexpected. It is known that morphine hardly influences persistent itching and that the die-away phase of the effect of an injection with morphine is occasionally accompanied with itch reactions.

The method of intracisternal injection is feasible in all animals which are able to tolerate cisternal puncture. In addition to cats, I used for this test rats, guinea pigs, rabbits and dogs. Use of the first two listed species entails technical difficulties. Dogs do not tolerate the injection well. It is easiest to carry out the test in rabbits, but in cats the length of the pruritus attack is greatest and most intensive and the disparity between the itch-inducing and the cramp-inducing dose is prarticularly large.

Apart from morphine and its derivatives, other reagents can be used to induce itching attacks. The incubation period and the persistence and intensity of the attack vary, depending on the nature of the injected reagent and the species of animal employed.

It should be pointed out that itching attacks are also a component of the picture which characterizes anaphylactic shock.

Aubrun[6] reported hyperesthesia and pruritus in the outer circumference of the affected dermatome following the scission of its sensory

6. Aubrun, E. A.: Prurit et hyperesthésie par section nerveuse, Compt. rend. Soc. de biol. **111**:404, 1932.

roots in the cervical region of the vertebral column. These observations are primarily of theoretic interest.

It is clear that the material available is sufficient to form a basis for the consistent production of prolonged pruritus in experiments with animals.

This test technic has been employed by me in experiments dealing with: (1) the nerve tracts of the itch-scratch reflex, (2) the nature of the substances which cause itching and the question of the existence among them of common features whereby the treatment of such substances as a group could be justified, (3) the site of action of these substances in the central nervous system, (4) the question of the existence of metabolites which evoke an itch reaction, (5) the explanation of pruritus in diabetes, and (6) the use of tests in animals for the evaluation of the therapeutic effect of medicaments in pruritus. (The last two items will be discussed in a later article.)

## NERVE TRACK OF THE ITCH-SCRATCH REFLEX

The theory of von Frey,[7] in which the skin is assumed to be equipped with a specific spatially discrete receptor for each quality of cutaneous sensation, is widely accepted. Specific itch receptors have not been demonstrated (Töröck[8]). It was shown by von Frey that stimulation of pain receptor points with a hair elicits itching. The identity of the terminal receptor sites of the skin in the 2 cases suggests that itch stimulus is a constituent of pain sensation. According to this conception itching is a modification of pain.

Several objections to this view have been advanced, and a separation of itch and pain sensations has been urged. The two sensations can be felt simultaneously and remain distinguishable even when they are so reduced in intensity as to be barely perceptible. Patients often consider itching to be even less tolerable than pain, particularly because of the general feeling of malaise which the former produces. The separation of these two sensations is also justified on objective grounds. In contrast to pain, itch stimulus elicits a rhythmically recurring reflex scratching movement. This reflex is not elicited by a single stimulus, but only by a summation of stimuli (Sherrington[1]). Whereas, immersion of the hand in a water bath with a temperature of 40 to 41 C. alleviates itching, the same treatment aggravates

7. von Frey: Physiologie der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, pt. 2.

8. Török, L.: Ueber das Wesen der Juckempfindung. Ztschr. f. Psychol. **46**:23, 1907.

burning pain (Lewis[9]) and (Lewis and Hess[10]). Pain, but not itching, can be elicited on cutaneous sites which have been denuded of epithelium. The response of itching to medicaments is distinct from that of pain. The best sedative, morphine, fails to alleviate itching; on the other hand, barbituric acids are less effective against pain than against pruritus. Ehrenwald and Koenigstein[11] examined the reactions of neurotic patients with symptoms of sensory disturbances of a dissociative character. They were able in some cases to elicit itching in patients who failed to register pain. Lewis[9] concluded his investigations of itching and pain as follows: "Thus there is abundant evidence that, though similarly produced, itch and pain are separate phenomena."

Rothman[12] has brought forward a theory to explain the contradictory facts. He accepted Head's[13] view according to which two separable forms of pain are distinguished, and gave anatomic observations by Gasser and Erlanger[14] in support of this conception. Rothman differentiated between sharply localized epicritic pain ("first pain") and diffuse protopathic pain ("second pain"). Rothman further confirmed Gasser and Erlanger's observation, that the epicritic pain is a function of thicker fast-conducting myelinated fibers, which Gasser and Erlanger called A and B fibers, while the protopathic pain is a function of thinner slow-conducting unmyelinated fibers, C fibers. Itching is regarded as a protopathic pain sensation, and "whether tickling, itching or protopathic pain sensation is felt depends only on the frequency of impulses in the slow conducting fibers" (Baird, Lever and Spies[15]).

Walshe,[16] among others, opposed this dual theory of pain sensation.

---

9. Lewis, T.: Pain, New York, The Macmillan Company, 1942.

10. Lewis, T., and Hess, W.: Pain Derived from Skin and Mechanism of Its Production, Clin. Sc. **1**:39, 1933.

11. Ehrenwald, H., and Koenigstein, H.: Klinische und experimentelle Untersuchungen über das Juckgefühl, Wien. klin. Wchnschr. **42**:1397, 1929.

12. Rothman, S.: Physiology of Itching, Physiol. Rev. **21**:357, 1941. Rothman, S., and Flesch, P.: The Physiology of the Skin, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1944, vol. 6, p. 195.

13. Head: A Case of Huntington's Chorea, Brain **28**:98, 1905.

14. Gasser, H. S., and Erlanger, J.: Role Played by Sizes of Constituent Fibers of Nerve Trunk in Determining Form of Its Action Potential Wave, Am. J. Physiol. **80**:522, 1927; Role of Fiber Size in Establishment of Nerve Block by Pressure of Cocaine, ibid. **88**:581, 1929.

15. Baird, P. C., Jr.; Lever, W. F., and Spies, T. D.: The Physiology of the Skin, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1942, vol. 4, p. 171.

16. Walshe, F. M. R.: Anatomy and Physiology of Cutaneous Sensibility: Critical Review, Brain **65**:48, 1942.

Besnier, Brocq and Jacquet[17] made an original attempt to explain the peculiarities of itch sensation. They related itch sensation to the sympathicus. At the same time that this view was suggested, my knowledge of the sympathetic system was still very little. Kroner[18] likewise ascribed the origin of itch sensation to a stimulus of sympathetic fibers. Winkler,[19] on the basis of experiments with human beings, associated itching sensation with vasomotor excitation. Brack[20] made a study of the relation of itching to the vegetative system. This author placed emphasis on itch preparedness, which he assumed to be an essential condition for the realization of the itching sensation. Itch preparedness is related to alimentary hemoclasia and responds in the same manner as the latter. The vegetative disturbance is expressed in the skin during an itching attack by a specific surface reaction of the cutaneous vessels.

The opinion was expressed by von Frey, who postulated only the identity of the terminal receptor of pain and itching, that it is possible that itching leads to the scratch reflex via a vegetative tract.

## RESULTS OF STUDIES

The participation of the autonomic nervous system in the itch reflex was examined by pharmacodynamic test methods[2]. In view of considerations which have been advanced, ergotamine tartrate ("gynergin") was employed to combat pruritus in dogs which received thalassin. Ergotamine tartrate is most certainly effective when administered intravenously. It prevents the itching attack if given before thalassin and rapidly suppresses an attack which has already started. A further merit of this reagent is the long persistence of its action. Animals that were given injections with ergotamine tartrate often remained without response to thalassin for several days. In early experiments we obtained this result with ergotamine tartrate only when it was injected into the blood stream, but later we also succeeded in obtaining resistance to thalassin in the dog by a prolonged prior treatment, consisting of a course of subcutaneous injections of ergotamine tartrate (0.5 mg.) twice daily.

---

17. Besnier, E.; Brocq, L., and Jacquet, L.: Troubles de la sensibilité, in Pratique dermatologique, Paris, Masson & Cie, 1904, vol. 4, p. 330.

18. Kroner, K.: Ueber den Juckreiz, Klin. Wchnschr. **3**:351, 1924.

19. Winkler, F.: Studien über das Zustandekommen der Juckempfindung., Arch f. Dermat. u. Syph. **99**:273, 1909.

20. Brack, W.: Die Bedeutung des vegetativen Systems für die Entstehung des Juckens, in Deliberationes dermatologorum internationalis IX-i, Budapest, 13-21 Septembris, 1935, Leipzig, Johann Ambrosius Barth, 1936.

The dosage of ergotamine tartrate was relatively large, 1 mg. per 7 to 10 Kg. of body weight of a medium-sized dog. The possibility seemed worth consideration that ergotamine tartrate is toxic as well as sympathicolytic. In order to examine this possibility, experiments were carried out with yohimbine chloride, which, despite the difference in its point of attack, shows the same effects on the autonomic system as ergotamine tartrate. Yohimbine chloride, administered intravenously (0.01 Gm.), produced the same effect as ergotamine tartrate.

All other tested adrenergic or cholinergic agents (epinephrine, ephedrine, pilocarpine compound, physostigmine salicylate and atropine) which stimulate or inhibit the autonomic system were without effect on the itch-scratch reflex elicited by intravenous injection.

Agents which inhibit the adrenergic fibers were observed in the experiments to suppress itch stimulus.

In order to extend and corroborate these observations, experiments were conducted with dogs in which large or small sections of the sympathicus had been eliminated. As scratching in dogs is largely, if not exclusively, centered on the head, the ganglion supremum was extirpated unilaterally or bilaterally in a series of 7 animals in order to eliminate sympathetic innervation of the head skin. In 1 dog the thoracic sympathetic trunk was removed. The interval which elapsed between the day of the operation and the itch test varies between two weeks and several months. In all the animals the opic effects associated with the removal of the ganglion were clearly in evidence. After unilateral elimination of the ganglion supremum, itching attacks failed largely, or completely, to involve the denervated side of the head. In every case the main effort of the scratching limb was directed to the normal side of the head. As regards other parts of the body, no directional preference was noticeable.

In a dog whose ganglions had been extirpated bilaterally, the following observations were made: Almost immediately after an injection, intensive scratching began. It did not, however, extend to the head zone; the animal did not rub its muzzle against the ground or between the forelegs, although this method of relief is common in dogs suffering from itching.

Further elucidation of the relationship of the sympathicus to scratching in the dog is offered by observations on a dog whose thoracic sympathetic trunk had been removed unilaterally. A dose of 0.1 cc. of thalassin sufficed in such an animal to induce a series of severe scratching attacks. The dog scratched uniformly only on the side of the body in which the sympathicus was intact. It rubbed its muzzle in a forward direction against a wall. The same animal presented a different picture five days later, when a larger dose (0.25 cc.) was

injected. The augmented dose elicited a severe scratching attack which involved both sides of the body equally. This paroxysm was followed by a brief interval during which the dog, under the toxic influence of thalassin, rested motionlessly on the ground. When the animal recovered, scratching was resumed and, as in the first experiment, was directed exclusively to the healthy side of the body.

These results further support the conception that sympathetic fibers play a part in the realization of the itch-scratch reflex. The role of the sympathetic fibers is, however, largely overshadowed when the itch paroxysm is of a severity which leads to a breakdown of the ordinary functional controls.

Small amounts of thalassin injected into the caudal vein of mice lead occasionally to scratching attacks, which, however, soon pass into fatal cramp attacks. In the experiments with mice, therefore, a different technic was employed. The animals were sensitized to light with hematoporphyrin. A water-cooled projection lamp served as the source of light. To elicit scratching of an intensity which clearly differentiates it from accidental scratching, a subcutaneous injection of 0.05 to 0.01 Gm. of the sensitizing substance was necessary. Twenty to thirty minutes after the injection the animals were exposed to light. If a clearcut scratching response was noted following this treatment, the injection of a sympathicolytic substance by a subcutaneous or intravenous route was undertaken. Control experiments with normal mice were carried out.

Mice tolerate ergotamine tartrate in almost any dosage, but are sensitive to yohimbine chloride. The results of 10 experiments are consistent with the interpretation that ergotamine tartrate and yohimbine chloride alleviate itch attacks.

These observations are not adequately explained by the existing anatomic knowledge of the nervous system. The present views on "vegetative sensitivity" are based on observations of internal organs. The existence of afferent autonomic fibers, which are indispensable for the participation of the sympathicus in the itch-scratch reflex, is still under discussion. Lenander,[21] Morley[22] and Lewis[9] expressed the opinion that the theory of the existence of afferent autonomic fibers has been excluded. In a recent review White and Smithwick[23] revived the theory of transmission of sensation via a sympathetic fiber. They formulated this view: "By means of axon reflexes sympathetic fibers

21. Lenander, K. G.: Ueber die Sensibilität der Bauchhöhle und über locale und allgemeine Anästhesie bei Bruch und Bauchoperationen, Zentralbl. f. Chir., 1901.

22. Morley, J.: Abdominal Pain, Edinburgh, E. & S. Livingstone, 1931.

23. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System: Anatomy, Physiology and Surgical Application, ed. 2, New York, The Macmillan Company, 1941.

may bring about superficial vasoconstriction, contraction of the erectopilae muscles, and possibly a production of irritant metabolites, thereby causing a painful stimulation of the cutaneous sensory nerves (proof uncertain)." With this remark the authors approach the opinion of Makenzie (cited by Lewis[9]). Whatever the outcome of this controversy, the fact that pain originates from sympathetic ganglions and can be eliminated by the removal of the latter is hardly in question.

The Dale hypothesis, according to which nerve fibers should be classified independently of their anatomic situation but according to their sensitivity to particular reagents, either as adrenergic or as cholinergic, should provide the simplest explanation of these phenomena. It seems reasonable to conclude that the itch-scratch reflex can be inhibited in an adrenergic fiber.

The successful results of treatment in animals conform well with the favorable clinical observations. The latter are not, however, so clearcut since it is necessary in treating pruritus to consider the advanced age of most of the patients and to restrict the dosage accordingly. Moreover, it is necessary to employ a subcutaneous rather than an intravenous route of injection. For treatment of pruritus in aged men, I prefer to use yohimbine chloride, in view of the beneficial effect of some components of this preparation on the blood supply to the genital system.

*Itch Attacks Induced by Intracisternal Injection of Morphine and Various Other Substances.*—The cat responds to injections of small doses of morphine (0.7 mg. per kilogram of body weight) into the cisterna cerebellomedullaris with extremely severe and prolonged itching (Mehes[5]). It can be shown that this effect can also be obtained with other animals (dog, rabbit and guinea pig). I sought to make use of cats in the evaluation of the utility of ergotamine tartrate in the relief of pruritus. The success was by no means equal to expectation. The drug was without injurious effect when injected intravenously in a high dosage into cats, but failed when given either intravenously or intracisternally to prevent or suppress an attack of itching.

Ergotamine tartrate injected into the cisterna not only did not prevent the onset of the attacks but actually appeared to augment them. This does not mean that the drug is able by itself to elicit pruritus when injected into the cisterna. Its direct action on the central nervous system is, however, of interest for another reason: cats, following an intracisternal injection of ergotamine tartrate, enter into a catatonic state similar to that induced by bulbocapnine.

Failure to control itching due to an injection of morphine solution with ergotamine tartrate was also recorded in the experiments with dogs and rabbits.

The surprising disparity between the results obtained with ergotamine tartrate in the experiments in which thalassin and morphine, respectively, were used cannot be explained on the basis of variation in species. Thus, in the dog ergotamine tartrate suppressed pruritus when this was induced by an intravenous injection of thalassin, but failed to suppress the pruritus when this was produced by intracisternal injection of morphine. The same general result was obtained with rabbits.

Ergotamine tartrate is, therefore, effective against the pruritus-inducing agent when the latter exerts its action via the circulatory system and is indifferent toward an agent when the agent attacks the central nervous system directly. It is clear that the sensible afferent fiber is not involved when the stimulating solution is allowed to flow into the cisterna. When, on the other hand, the stimulant is allowed to circulate in the blood stream, as after an intravenous injection, it is able to act peripherally. The fibers which carry the itch stimulus along a part of its way and which respond adrenergically may be situated in this centripetal track. It is implicit in this view that ergotamine tartrate is an inhibitor of the peripheral itch stimulus and that it is without action on a centrally elicited itch attack.

Experiments with cats were carried out in which the sympathicus had been eliminated surgically. This type of experiment was particularly impressive when performed with the cat, as in this animal scratching was normally restricted under these conditions to the head area exclusively, so that removal of the ganglion supremum put all fibers supplying the field of scratching completely out of action. The surgical intervention was unilateral in one series and bilateral in a second series of cats. After intervals of varying length the animals were given an effective dose of morphine intracisternally. In no case was a noteworthy diminution of the scratch paroxysm induced.

*Properties Common to Substances Which Elicit Pruritus by Intracisternal Injection.*—The response elicited in the dog by intravenous injection of thalassin was designated as the itch-scratch phenomenon. The view that this animal experiences a subjective sensation of itching seems to be justified by the following observations. Contact of the skin with thalassin produced itching and sometimes evoked itching eruption. As soon as thalassin began to act in the dog, the animal jumped to its feet, with every sign of a sense of severe discomfort, turned in a circle, howled and attempted to alleviate the disagreeable feeling not only by scratching but also by rubbing its hide against a

solid object. It behaved as if it were actually suffering from some cutaneous outbreak of a type which in human beings is accompanied with itching. When, on the other hand, the scratch reaction was elicited by the intracisternal method, the scratch motions so predominated as to render it difficult to make any specific assumption with regard to the sensation of the animal. In subsequent discussion, therefore, there will be reference to this type of response not as an itch reflex but as a scratching paroxysm.

It will be shown that the action of morphine is not singular to this reagent but common to a large number of different substances injected intracisternally. The dose of reagent generally rates a few milligrams per kilogram of body weight, or less. The concentration of the solution must be so chosen that the total volume injected does not exceed 0.3 cc., in order that a sudden augmentation of the cerebrospinal fluid pressure will not result. When this rule could not be observed in practice, the difficulty was overcome by removing from the liquor before the injection an amount of fluid equivalent to the excess subsequently injected.

Although the participation of the sympathicus in the scratch reflex had not been shown by the intracisternal method just described, further experiments on the effect of the sympathicotropic and vagotropic substances when injected into the cisterna cerebellomedullaris were undertaken. Epinephrine, "sympatol" ([para-hydroxyphenyl] methylaminoethanol tartrate) and ephedrine proved to be without effect. On the other hand, members of the muscarine group—pilocarpine and physostigmine compounds and acetylcholine—acted as scratch stimulants. The remarkably high dilution in which physostigmine continued to exert scratch-eliciting action is noteworthy. This substance failed to act only in dilution of 1 to 10,000,000. Physostigmine compound enhanced the reaction to acetylcholine in the conditions of these experiments.

Posterior pituitary injection ("pituitrin"), which possesses a somewhat similar affinity for the autonomic nervous system (Cushing[24]), failed completely to elicit scratching.

Since drugs of the muscarine group elicit scratching, the possibility that they exhibit this property because of a cholinergic action required consideration. This conception had to be abandoned, however, when it was observed that the cholinergic antagonist, atropine, which resembles a rheostat in its action on vagus stimulants, failed to inhibit or to weaken the action of the substances of the muscarine group and, in fact, acted itself as a pruriginous substance. Atrophine in small doses elicited scratching when administered intracisternally.

24. Footnote deleted.

In view of these experimental results, recent clinical observations gain added interest. Grant, Pearson and Comeau,[25] Hopkins, Kesten and Hazel[26] and Nomland[27] observed patients who suffered from urticaria and in part from generalized itching. The symptoms occurred after intense effort, heat or excitement. The authors concurred in the view that subcutaneous injections into these patients of an acetylcholine derivative could elicit the same symptoms. Atropine failed to oppose this action.

It must be considered that the previously mentioned substances have not only a cholinergic action but also the ability to stimulate the central nervous system.

The detailed study of this point has yielded one further result of interest. The experimental result depends on the dosage employed. There seems to be only a slight difference between the dose which elicits scratching and that which produces cramps. The transition as the dose is increased is as follows: At the critical dose level, the normally scratching animal suddenly begins to suffer from twitching and then from cramps, which after a short time recede, leaving the field free again for rhythmic scratching. With a larger dose, cramps are induced directly following the injection or following a longer latent period in which scratching does not occur. Scratching can follow the cramp attack in these cases as well.

A combination of subthreshold doses of pruritus-inducing substances elicits scratching. When two such substances are combined in doses, each of which separately elicits scratching, cramps are induced which become manifest in most cases only after a prolonged latent period.

A consideration of the list of reagents which have proved effective in such tests emphasizes two facts: The effective agents are all substances which stimulate the central nervous system, and in high dosages they cause cramps.

In order to extend the basis of these conclusions, it was necessary to test substances which are indubitably of the character of cramp poisons. In this group belong among others: strychnine, caffeine, camphor, pentamethylenetetrazol, picrotoxin, thalassin, alizarin blue, potassium salts and ammonium salts. Nikethamide and lobeline, which attack the vomiting and breathing centers, were likewise in-

25. Grant, R. T.; Pearson, R. S. B., and Comeau, W. S.: Observations on Urticaria Provoked by Emotion, by Exercise and by Warming the Body, Clin. Sc. **2**:253, 1936.

26. Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**:679 (Nov.) 1938.

27. Nomland, R.: Cholinogenic Urticaria and Cholinogenic Itching, Arch. Dermat. & Syph. **50**:247 (Oct.) 1944.

cluded in this group. The list given is not, of course, an exhaustive one. With all the substances it proved possible, by careful control of dosage, to elicit separately scratching as well as cramps. Minute variation in dosage at the critical level determines the form in which the stimulation of the nervous system manifests itself.

The experiments reported herein show that the pruriginous agents contain a cramp-producing component. Although these substances possess different chemical compositions and therapeutic actions and even though they act in some cases as mutual antidotes, they form a uniform group from the standpoint of the present investigation. So far as these experiments showed, the scratch paroxysm is a preliminary of cramps. In the light of this conclusion the pruritus effect of morphine and apomorphine occasions no surprise, since these agents are also cramp poisons.

*Site of Action of Pruritus-Inducing Reagents in the Nervous System.*—The central origin of the scratch response in animals which are intracisternally treated is indisputable. It is also possible to draw from the same experiments conclusions of a more specialized character, with regard to the site of origin of the scratch response. Relevant to this are certain observations which I made many years previously, and on the basis of which the use of a specific group of medicaments in the alleviation of itching was indicated. Pruritus can be alleviated in the first instance by brain stem soporifics. The affinity of this group of substances for particular portions of the brain provides indications of the localization of the itch stimuli. Many of the medicaments in question, including notably barbituric acid, attack the brain stem.[28]

A group of poisons which have already been listed in this paper elicit in animals in good general condition only scratch paroxysms of varying intensity, whereas, another group elicits salivary flow or vomiting in addition to scratching. On the other hand, a powerful emetic, such as apomorphine, or a reagent which promotes salivary flow, such as pilocarpine compound, can be grouped together with the pruriginous substances. The occurrence of vomiting or salivary flow concomitantly with the scratch paroxysm suggests the possibility that the centers of these activities adjoin one another. The position of the vomiting center within the medulla oblongata is known. Since the transition of a stimulus from the vomiting center to that of salivary excretion is a physiologic process, it seems probable that observation

28. Pick, E. P., and Mitarbeiter: Arch. f. exper. Path. u. Pharmakol., 1926-1930. Meyer, H. H., and Gottlieb, R.: Die experimentelle Pharmakologie als Grundlage der Arzneibehandlung, ed. 8, Berlin, Urban & Schwarzenberg, 1933, p. 57.

of salivary flow can give useful information with regard to the action of pruriginous substances.

It is, moreover, remarkable that pruriginous substances, as pentamethylenetetrazol, attack the brain stem.

A closer restriction of the site of the scratching center is provided by experiments with alizarin blue. For these experiments a dyestuff was chosen which elicits cramps and at the same time is able to stain tissues intensively, even in high dilution. The assumption that a cramp poison would act in suitable dosage as a pruriginous substance was corroborated. Alizarin blue is one of the most efficient scratch irritants. The path of its movements in the body, following an injection, is easily traced. The following data were obtained: A cat received an intracisternal injection with a suitable amount of dyestuff and was killed with an intracardial injection of chloroform immediately after a scratching response was observed. The stain had diffused rapidly through the subarachnoid space,[29] but had penetrated into the depth only in one place in the lower part of the medulla oblongata.

A number of incidental observations again directed attention to the medulla oblongata. In certain experiments, although attempts to puncture the cisterna failed, the cats scratched regularly after withdrawal of the needle. This phenomenon of scratching could be reproduced in the case of 1 animal, even after a considerable interval, simply by touching the ear. Histologic examination showed that, in these animals as well, wounding of the lower section of the medulla was responsible for the scratching.

When these observations are considered together, they appear to provide convincing support for the view that the site of attack of a pruriginous agent is the medulla oblongata. It will be my future objective to locate the site of origin of the scratch response in the central nervous system more accurately by means of operative procedure, which will make possible testing of the pruriginous agents in animals in which different parts of the nervous system have been eliminated.[30]

It is not proper in the context to explain the surgical methods in detail. It may be mentioned in general that cats can be treated by means of a Starling pump used intermittently with air or with a mixture of air and ether. This artificial combination of respiration and narcosis presents two distinct advantages: The narcotic dosage can

29. Hamperl, H., and Heller, H.: Die Ausbreitung intrazisternal injizierter Stoffe im Liquorraum, Arch. f. exper. Path. u. Pharmakol. **173**:283, 1933.

30. Königstein, H.: Ueber Lokalisationsversuche des durch Morphium ausgelösten "Kratzwerkes" in Centralnervensystem, Arch. internat. de pharmacodyn. et de thérap. **62**:1, 1939.

be so adjusted as to insure the awakening of the animal at any specified time, and, even more important, the administration of artificial respiration makes it possible to eliminate shock and respiratory paralysis, two common by-effects of lesions in the vicinity of the respiratory center. A further difficulty of experiments of this type is hemostasis. I sought to overcome the bleeding by throttling the carotid arteries and blocking vessels which open into the substantia spongiosa by using hot wax.

The influence of morphine in decerebrated cats persists for several hours, and there is, therefore, a sufficiency of time in the interval for the performance of complicated surgical procedures and for the observation of their results. The morphine solution is generally injected into the cisterna; if the latter happens to have been opened, the solution can be administered drop by drop into the rhomboid fossa; in special circumstances it can be injected into the central canal. I have observed that removal of the cerebrum does not affect the scratch phenomena. In successive experiments I removed the thalamus, the striatum and the pallidum and finally the entire midbrain up to the tentorium. The complete removal of the midbrain failed to weaken, but actually augmented, the intensity of the scratch paroxysms, although this operation leads to decerebration rigor because of the destruction of the nucleus ruber. This experiment suggests, therefore, that the removal of the midbrain eliminates restrictive influences.

The extirpation of the cerebellum was without effect on the scratching response.

In subsequent experiments, it was observed that the complete extirpation of all brain parts situated above the auditory nuclei does not prevent itch paroxysms.

In the aforementioned experiment, partial removal of the medulla oblongata was effected. The removal of further parts of the medulla oblongata is immediately followed by a disturbance of the course of the scratch paroxysm. Scission, in a caudal direction, of the corpus restiforme leads to a progressively increasing restriction of the scratch movements. It is clear, therefore, that the source of the scratching response must be sought in the under part of the medulla in a region bounded in the cranial limit by the auditory nuclei and in the caudal direction by the corpora restiforme.

*What Is the Role of the Sensory Nerves Supplying the External Ear in Itch Paroxysms?*—Scratching could be elicited in the interval between two postcritical scratching bouts by touching the animal on the ear. The sensory nerves of the external ear consist of roots of the trigeminus, of the vagus and of the upper cervical nerves. Wini-

warter[31] undertook the laborious task of effecting the scission of all these nerves at the point of their emergence from the central nervous system. When all these nerves are cut, the reflex of the ear disappears, but the spontaneous scratching paroxysms are unchecked. Winiwarter concluded that the scratching center, when it is stimulated by morphine, sends out impulses spontaneously as well as in response to sensory stimuli.

## REPORT OF EXPERIMENTS

In the following experiments, thalassin was injected intravenously. The scratching paroxysm following the injection was suppressed by the administration of ergotamine tartrate or yohimbine chloride (solution in water).

EXPERIMENT 1.—A dog weighing 7 Kg., was given 0.5 cc. of thalassin at 11:40 a.m. At 12.04 p.m., a typical scratching paroxysm occurred. The dog's general condition was good, but later it showed a tendency to drowsiness.

EXPERIMENT 2.—A cat weighing 2,500 Gm., was given 0.1 cc. of thalassin at 7:04 p.m. Scratching began at once.

In the following experiments, solution of morphine hydrochloride was administered intracisternally.

EXPERIMENT 3.—A cat, weighing 3,300 Gm., was given morphine solution, 0.7 mg. per kilogram of body weight, at 7:41 p.m. Scratching began at 7:44 p.m.

EXPERIMENT 4.—A cat, weighing 2,900 Gm., was given morphine solution, 0.7 mg. per kilogram of body weight, at 11:26 a.m. At 11:29, the scratching was severe and frequent and the body was thrown against the ground. Scratching lasted until 12:40 p.m.

EXPERIMENT 5.—A cat, weighing 3,200 Gm., was given morphine solution, 0.7 mg. per kilogram of body weight, at 11:30 a.m. At 11:40 a.m. scratching began, and at 6:10 p.m. scratching was severe and without variation.

EXPERIMENT 6.—A dog, weighing 10.9 Kg., was given morphine solution, 1.0 mg. per kilogram of body weight. After 10 minutes, severe scratching began and lasted 1 hour, accompanied with vomiting and defecation. After 24 hours, the dog's legs were unsteady.

EXPERIMENT 7.—A rabbit, weighing 2,300 Gm., was given morphine solution, 0.6 mg. per kilogram of body weight, at 11:15 a.m. At 11:24 scratching began; at 11:29 scratching could be elicited by touching the ear; at 11:35 there was spontaneous scratching, and at 11:43 a.m. and at 12.07 p.m. there was vehement scratching.

Thirty-nine per cent of success was obtained in a total of 32 experiments. The dose administered was 0.6 to 0.8 mg. per kilogram of body weight. The latency period lasted 4 to 14 minutes. The paroxysm lasted up to 42 minutes.

EXPERIMENT 8.—A guinea pig weighing 477 Gm., was given morphine solution intracisternally, 0.7 mg. per kilogram of body weight. At 11:24 a.m. scratching could be elicited by touching the ear; at 11:29 there was spontaneous scratching;

31. Winiwarter, F.: Ueber die pharmakologische Analyse des Ohrkratzreflexes, Arch. internat. de pharmacodyn. et de thérap. **62**:42, 1939.

at 11:32 scratching occurred when the animal was stimulated; at 11:36 there was a vehement spontaneous paroxysm, the animal throwing itself on its back; at 11:51 a.m. there was increasing torpor, and at 12:08 p.m. the animal slowly began to recover.

In the following experiments, the scratching paroxysm following the intravenous injection of thalassin was suppressed by the administration of ergotamine tartrate or yohimbine chloride (solution in water).

EXPERIMENT 9.—A dog weighing 8 Kg., was given 0.3 cc. of thalassin intravenously at 11:40 a.m. At 11:43 vehement scratching began. At 11:46, 0.0025 cc. of ergotamine tartrate was given intravenously. At 11:48 a.m. the drive to defecate and urinate appeared to be intensified, and there was vomiting, but no scratching. At 12:30 p.m., after the injection of ergotamine tartrate, there was no scratching.

EXPERIMENT 10—A dog weighing 7 Kg., was given 0.3 cc. of thalassin intravenously at 11:35 a.m. At 11:43 scratching began. At 11:47 0.0025 cc. of ergotamine tartrate was administered intravenously. At 11:49 a.m. the defecation drive was evident, with vomiting. At 12:10 p.m., after injection of ergotamine tartrate, no scratching paroxysm occurred.

EXPERIMENT 11.—A dog, weighing 8 Kg., received 0.0025 cc. of ergotamine tartrate intravenously on February 18, 24 and 26. After the third injection of ergotamine tartrate, no scratching could be elicited with thalassin during the next 3 days.

EXPERIMENT 12.—A dog, weighing 11.5 Kg., was given 0.5 cc. of thalassin intravenously at 6:10 p.m. At 6:12 the animal began to scratch; at 6:14, 4 mg. of yohimbine was given intravenously, and at 6:17 p.m. there was no scratching.

EXPERIMENT 13.—A dog was given 0.4 cc. of thalassin intravenously at 6:41 p.m. At 6:47 there was vehement scratching. After intravenous injection of 2 mg. of yohimbine, there was a short attack and then no scratching.

EXPERIMENT 14.—A dog, weighing 10 Kg., received 0.4 cc. of thalassin intravenously at 5:35 p.m. At 5:37 there was vehement scratching. At 5:40, 3 mg. of yohimbine was given intravenously. At 5:41 there was scratching, at 5:42 a defecation drive and at 5:51 no scratching. The dog was insensitive to thalassin even after 72 hours.

In the following experiments, operation was done on the sympathetic trunk.

EXPERIMENT 15.—A dog, weighing 10 Kg., was given 0.25 cc. of thalassin eighteen days after extirpation of the right superior cervical ganglion. After 10 minutes, a severe scratching paroxysm was presented, the right part of the head remaining unaffected.

EXPERIMENT 16.—A dog, weighing 12 Kg., underwent extirpation of the right superior cervical ganglion on July 22 and of the left superior cervical ganglion on September 15. Thalassin (0.25 cc.) was given intravenously on October 26. There was severe scratching after 8 minutes, the lateral parts of the head remaining unaffected. There was no attempt to rub the muzzle against the ground or the walls or between the paws.

EXPERIMENT 17.—A dog, weighing 12 Kg., underwent operation in which the thoracic aspect of the sympathetic trunk on the left side was removed on September 20. Thalassin (0.1 cc.) was given intravenously on November 1. The dog always scratched on the right side, mostly pressing the flank and muzzle in a forward direc-

tion against the wall. Five days later, the dog received an injection of 0.25 cc. of thalassin intravenously. The ensuing severe scratching paroxysm involved both sides of the body to an equal degree. The animal suddenly lay down and remained motionless, without showing any response for some time. After recovery, scratching was directed exclusively to the side on which the sympathicus was intact.

Ergotamine tartrate failed to suppress scratching paroxysms elicited by intracisternal injection of morphine solution.

EXPERIMENT 18.—A cat, weighing 2,800 Gm., was given an intracisternal injection of morphine solution, 0.7 mg. per kilogram of body weight, at 8:57 a.m. At 9:02 there was vigorous scratching at short intervals. At 9:13 a.m., 4.5 mg. of ergotamine tartrate was given intravenously. There was vehement scratching at 9:15, 9:16, 9:17, 9:18, 9:23, 9:29, and 9:32 a.m.

EXPERIMENT 19.—A cat, weighing 3,300 Gm., was given ergotamine tartrate intravenously, 0.25 mg. per kilogram of body weight, at 6:44 p.m., in conjunction with intracisternal injection of morphine (0.7 mg. per kilogram of body weight). At 6:51 p.m. a defecation and urination drive was evidenced, with salivation and trembling. At 7:03 there was a scratching paroxysm. At 7:26 p.m. the scratching paroxysm was recurring at widely spaced intervals.

EXPERIMENT 20.—A cat, weighting 2,100 Gm., was given 1.5 mg. of morphine solution and 0.25 mg. of ergotamine tartrate intracisternally at 6:20 p.m. At 6:28 there was a vehement typical scratching paroxysm. At 6:40 p.m. the scratching was continuous and vigorous.

EXPERIMENT 21.—A cat, weighing 2,600 Gm., was given 0.3 mg. of ergotamine tartrate intracisternally at 10:22 a.m. At 12 a.m., it had not yet scratched and its behavior was similar to that of an animal under light narcosis. It offered no resistance when it was laid on its side, and it could be hung free in the air by the forelegs like a cat that has been given bulbocapnine.

EXPERIMENT 22.—A dog, weighing 7,000 Gm., was given an intracisternal injection of morphine solution, 0.7 mg. per kilogram of body weight, at 6:15 p.m. At 6:53 there was vomiting and at 7 p.m. vigorous scratching. At 7:10 p.m., 2 mg. of ergotamine tartrate was given intravenously. At 7:15 the scratching paroxysm was still present. At 7:23 p.m., 2.5 mg. of ergotamine tartrate was given intravenously, and at 7:37 the scratching continued.

In the following 2 experiments, the stimulants used acted on the sympathetic nerve endings.

EXPERIMENT 23.—In a rabbit, weighing 1,000 Gm., the intracisternal administration of 0.1 to 0.5 mg. of epinephrine was inefficacious.

EXPERIMENT 24.—A cat was given 0.02 mg. of phenylephrine hydrochloride intracisternally at 6:23 p.m; at 6:37 p.m. nothing of significance had occurred.

In the following experiments, the stimulants used acted on the parasympathetic nerve endings.

EXPERIMENT 25.—A cat, weighing 2,300 Gm., was given an intracisternal injection of 2 mg. of pilocarpine hydrochloride at 9:35 a.m. Scratching began at 9:36 and was continuous at 9:37, vigorous at 9:42 and continuous at 9:45 a.m. At 9:48 retching and salivation occurred. Scratching lasted until 10:41 a.m.

EXPERIMENT 26.—A rabbit, weighing 1,000 Gm., was given 6 mg. of pilocarpine hydrochloride intracisternally at 12:37 p.m. At 12:42 p.m. scratching was vigorous

and continuous on both sides. Scratching and salivary secretion were observed at 12:45, at 12:53 and at 12:56 p.m. The animal rubbed its muzzle on the ground.

EXPERIMENT 27.—A cat, weighing 2,100 Gm., was given physostigmine salicylate intracisternally, in dilution of 1 to 1,000,000 (0.1 cc. per kilogram of body weight), at 8:55 a.m. Scratching was observed at 8:55 and at 9:17 a.m.

EXPERIMENT 28.—A rabbit, weighing 1,000 Gm., was given 0.3 cc. of physostigmine salicylate intracisternally, in dilution of 1 to 10,000, at 10:39 a.m. Scratching was observed at 10:46, 10:48, and 10:50, 10:51 and 10:55 a.m.

EXPERIMENT 29.—A cat, weighing 2,400 Gm., was given 0.03 mg. of acetylcholine intracisternally at 8:35 a.m. At 8:41 several successive scratching episodes were observed.

EXPERIMENT 30.—A cat, weighing 2,500 Gm., was given an intracisternal injection of 0.03 mg. of acetylcholine and 0.4 cc. of physostigmine salicylate (in dilution of 1 to 10,000,000) at 9:31 a.m. Scratching began immediately and was continuous until 9:41 a.m.

EXPERIMENT 31.—A cat, weighing 3,000 Gm., was given 0.5 mg. of atropine sulfate intracisternally at 7:25 p.m. Scratching began immediately and continued for 10 minutes.

EXPERIMENT 32.—A cat, weighing 1,900 Gm., was given 1 mg. of atropine intracisternally at 5:39 p.m. Scratching was observed at 5:41, 5:46 and 5:50 p.m. At 5:55, it was observed that the animal scratched frequently and was in poor general condition. Scratching occurred at 6 p.m., 6:05 and 6:08, at which time the animal became excited. At 6:15 cramps occurred, and at 6:25 p.m. the animal recovered.

EXPERIMENT 33.—A cat, weighing 2,400 Gm., was given 2 mg. of pilocarpine hydrochloride and 2 mg. of atropine intracisternally at 6:32 p.m. At 6:52 the animal had cramps, and at 7:05 p.m. it recovered.

EXPERIMENT 34.—A cat, weighing 2,650 Gm., was given 0.5 mg. of atropine and 0.1 mg. of physostigmine salicylate intracisternally at 6:43 p.m. Scratching occurred at 6:44, 6:46, 6:47 and 6:49 p.m.

EXPERIMENT 35.—A cat, weighing 2,300 Gm., was given 0.7 mg. of morphine solution intracisternally at 6:10 p.m. Scratching was observed at 6:13 and at 6:16 p.m. At 6:27, 2 mg. of atropine was given intracisternally. Scratching occurred at 6:29, 6:30, 6:32, 6:35, 6:36 and 6:41 p.m. and cramps at 6:47, 6:55 and 7:05 p.m.

In the following experiments, the stimulants acted on the central nervous system.

EXPERIMENT 36.—A cat, weighing 1,900 Gm., was given 0.03 mg. of strychnine nitrate intracisternally at 6:16 p.m. Scratching was observed at 6:22 p.m. and vigorous scratching at 6:23. At 6:40 p.m. the animal became hyperexcitable.

EXPERIMENT 37.—A cat, weighing 1,700 Gm., was given 0.04 mg. of strychnine intracisternally at 6:46 p.m. Distinct scratching was observed at 6:47 p.m., and at 6:48 the animal became stiff. At 6:50 cramps occurred, and at 6:51 attempts at scratching were frustrated in part by rigor. At 6:54 the animal was scratching its neck.

EXPERIMENT 38.—A cat, weighing 2,600 Gm., was given an intracisternal injection of caffeine and sodium benzoate (2 mg. per kilogram of body weight) at 5:49 p.m. At 5:50 the animal scratched, and at 5:54 it scratched and shook its head. At 5:53 p.m. it scratched, but was in good general condition. At 5:54 it wiped its muzzle; at 5:55 it shook its head and scratched; at 5:57 and at 6 p.m. there was persistent severe scratching. At 6:10 p.m. scratching was observed to continue.

EXPERIMENT 39.—A rabbit, weighing 1,100 Gm., was given 7.5 mg. of caffeine intracisternally at 2:47 p.m. Immediate and continuous scratching was observed.

EXPERIMENT 40.—A rabbit, weighing 1,080 Gm., was given 2 mg. of caffeine intracisternally at 11:56 a.m. Scratching occurred immediately, followed by cramps.

EXPERIMENT 41.—A cat, weighing 2,450 Gm., was given 0.4 cc. of camphor (10 per cent solution in oil) intracisternally at 6:04 p.m. Scratching on both sides was observed immediately and continuously. At 6:11 p.m. the animal scratched vigorously at short intervals. Scratching was observed at 6:16, 6:19, 6:33 and 6:50 p.m.

EXPERIMENT 42.—A rabbit, weighing 1,000 Gm., was given 0.1 cc. of camphor (20 per cent solution in oil) intracisternally. After a few minutes continuous scratching was observed.

EXPERIMENT 43.—A rabbit, weighing 1,000 Gm., was given 0.2 cc. of camphor intracisternally. Frequent respiration was observed, and after a few minutes the animal fell asleep.

EXPERIMENT 44.—A cat, weighing 2,600 Gm., was given 0.2 cc. of pentamethylenetetrazol (10 per cent solution in water) intracisternally at 6:42 p.m. Cramps were elicited immediately after administration of the drug, and scratching was observed at 6:49 and 6:50 p.m.

EXPERIMENT 45.—A cat, weighing 2,100 Gm., was given 0.05 mg. of picrotoxin intracisternally at 5:55 p.m. Vehement scratching was observed at 6:05, 6:06 and 6:08 p.m. and continued for some time.

EXPERIMENT 46.—A cat, weighing 2,100 Gm., was given 0.06 mg. of picrotoxin intracisternally at 6:35 p.m. At 6:39 scratching was observed and at 6:40 a vehement scratching paroxysm. At 6:45 the animal scratched with the highest intensity. Retching occurred, and there was frequent respiration at 6:48, with cramps at 6:53 p.m.

EXPERIMENT 47.—A cat, weighing 3,200 Gm., was given 0.12 cc. of thalassin intracisternally at 7:05 p.m. At 8 p.m. vehement and continuous scratching was observed.

EXPERIMENT 48.—A cat, weighing 3,000 Gm., was given thalassin intracisternally, 0.1 cc. per kilogram of body weight, at 6:35 p.m. Scratching, alternating with cramps, was observed immediately.

EXPERIMENT 49.—A cat, weighing 3,100 Gm., was given 0.1 mg. of alizarin blue intracisternally at 7:02 p.m. At 7:05 the animal scratched with a foreleg. At 7:08, 7:09, 7:10, 7:11, 7:14 and 7:16, it scratched vigorously with a hindleg. At 7:21 the animal scratched with the same intensity as did animals after the administration of morphine. At 7.23 p.m. the mouth was opened widely and the enimal engaged in licking. At 7:30 p.m. the animal became excited.

EXPERIMENT 50.—A cat, weighing 2,500 Gm., was given 0.5 per cent potassium chloride intracisternally, 0.2 cc. per kilogram of body weight, at 6:49 p.m. Scratching occurred immediately, and by 7:14 p.m. it was observed to be continuous.

EXPERIMENT 51.—A cat, weighing 2,300 Gm., was given 0.5 per cent potassium chloride intracisternally, 0.25 cc. per kilogram of body weight, at 6:42 p.m. At 6:44 p.m. there were continuous cramps, with scratching. At 6:54 p.m. the animal was still scratching.

EXPERIMENT 52.—A cat, weighing 2,100 Gm., was given 1 per cent potassium chloride intracisternally, 0.1 cc. per kilogram of body weight, at 2.23 p.m. At 2:26 p.m. scratching was observed. It was continuous at 2:30 and vigorous at 2:31. At 2:34 the animal responded with scratching when stimulated, and scratching ceased at 2:40 p.m.

EXPERIMENT 53.—At 11:20 a.m., a rabbit, weighing 1,200 Gm., was given an intracisternal injection of 1.2 per cent solution of potassium sulfate equimolecular to 1 per cent potassium chloride solution, 0.3 cc. per kilogram of body weight. Scratching was continuous from 11:21 until 11:29 a.m.

EXPERIMENT 54.—A cat, weighing 2,100 Gm., was given an intracisternal injection of 0.7 per cent solution of ammonium chloride, 0.2 cc. per kilogram of body weight, at 12:22 p.m. At 12:23, vigorous scratching began and continued until 12:33 p.m. At 12:44 p.m. scratching could be elicited by touching the ear.

EXPERIMENT 55—A rabbit, weighing 1,470 Gm., was given an intracisternal injection of 0.7 per cent solution of ammonium chloride, 0.3 cc. per kilogram of body weight, at 11:37 a.m. At 11:38 it was observed that scratching occurred at short intervals on both sides and lasted up to 10 minutes.

EXPERIMENT 56.—A rabbit, weighing 1,000 Gm., was given an intracisternal injection of 0.3 cc. of ammonium sulfate solution equimolecular to 0.7 per cent solution of ammonium chloride at 11:30 a.m. Scratching was ilicited at 11:32 a.m.

EXPERIMENT 57.—A cat, was given 0.05 cc. of nikethamide ("coramine"), 25 per cent solution in water, intracisternally. Scratching began immediately.

EXPERIMENT 58.—A cat, weighing 3,000 Gm., was given 0.25 cc. of nikethamide intracisternally at 6:50 p.m. The animal immediately became excited, presenting bloody foaming at the mouth, spasmic contraction of the eyelids and jowls, flow of tears and cramps.

EXPERIMENT 59.—A cat, weighing 2,700 Gm., was given 0.1 mg. of lobeline intracisternally at 6:21 p.m. Vomiting occurred at 6:22 p.m. At 6:35 p.m. the animal recovered and responded to stimulation by scratching.

## SUMMARY AND CONCLUSIONS

The present investigation describes experiments on the use of animals for the study of pruritus. Methods are described which make it possible to use animals for this purpose.

Scratching paroxysm could be induced by intravenous injection of thalassin in dogs, by sensitization of white mice against light with hematoporphyrin and by injection of morphine solution and other substances into the cisterna cerebellomedullaris. The last-named method has been applied in cats, dogs, rabbits and guinea pigs.

An attempt is made to answer the following questions by means of experiments with animals:

1. What are the nerve tracks of the itch-scratch reflex?

2. How are the pruriginous substances formed, and have they properties in common by which they may be collected into a single group?

3. Where in the central nervous system should the site of action of pruriginous substances be sought?

Differentiation is made between itching and pain on the basis of previous results. The relation between the itch-scratch reflex and the autonomic nervous system is discussed. A scratching paroxysm induced by intravenous injection of thalassin in the dog can be prevented or suppressed by ergotamine tartrate or yohimbine chloride. All other adrenergic or cholinergic substances which stimulate or

inhibit the autonomic nervous system fail to affect the itch-scratch reflex in the aforementioned experiments.

In further experiments with dogs, larger and smaller parts of the sympathicus were eliminated by unilateral or bilateral operations. The results of these trials support the conclusion that sympathetic fibers play a part in the conduction of the itch-scratch reflex.

White mice were sensitized with hematoporphyrin and exposed to light. When regular scratching ensued, a sympatholytic substance was injected. The results of 10 experiments suggest that ergotamine tartrate and yohimbine chloride exert a depressant effect on the scratching paroxysm.

These observations are discussed in the light of existing knowledge concerning "vegetative sensitivity."

Clinical use of ergotamine tartrate and yohimbine chloride for the treatment of pruritus yielded satisfactory results. Ergotamine tartrate is without effect on pruritus induced in animals by intracisternal injection of various substances. The effectivity of the drug is dependent on the site of the action of the pruriginous substance. Substances injected into the cisterna exert a central action; substances injected intravenously probably exert a peripheral action. Adrenergic fibers which are paralyzed by ergotamine tartrate and yohimbine chloride may exist in the peripheral zone.

Scission of the sympathicus in the cat is without effect on the scratching paroxysm which is induced by intracisternal injection.

An extensive series of substances of different chemical nature which elicit pruritus when injected intracisternally is given. All members of the series are central stimulants and in high dosage elicit cramps.

The following observations suggest that the medulla oblongata contains a scratch center. Substances (soporifics for the brain stem) which affect the brain stem, e.g., barbituric acids, are particularly suitable for the treatment of pruritus.

Some of the pruriginous reagents are also stimulants of salivation and vomiting. This circumstance suggests that the responsible centers are similarly situated.

Alizarin blue is a dye which has a strong affinity for tissues and also acts as a pruriginous and cramps-producing substance. When it is injected intracisternally and elicits itching paroxysm, it accumulates in a certain location in the lower part of the medulla oblongata.

Systematic elimination of different parts of the brain leads to the conclusion that a scratching center is situated in the lower part of the medulla oblongata. It is bounded cranially by the auditory nuclei and caudally by the corpora restiforme.

26 Bialik Street.

# TREATMENT OF HYPERHIDROSIS AND SYMMETRIC LIVIDITIES OF THE FEET

J. GARDNER HOPKINS, M.D.
ARTHUR B. HILLEGAS, M.D.
R. BRUCE LEDIN, M.D.
GERBERT C. REBELL, M.D.
AND
EARL CAMP, M.D.
NEW YORK

IN THE course of a study of dermatophytosis in the infantry troops at Fort Benning, Ga., numerous cases of severe inflammation of the feet were encountered which could not, on the basis of our evidence, be ascribed to fungous or to pyogenic infection or to sensitization to footgear. It appeared that the essential cause was hyperhidrosis. The cases were of two types.

## DIFFUSE HYPERHIDROSIS

The larger group was of men who showed excessive sweating of the entire foot. The skin was often macerated. There was frequent erythema and edema of the dorsal and plantar surfaces of the toes and often denudation of the corneal epithelium and fissures on the webs of the toes. In a number of men definite nonsuppurative cellulitis of the toes developed. All toes were uniformly involved, and the complaints of the men were of burning and pain rather than of itching.

In 201 such cases fungi were demonstrated in only 37 per cent, although some were searched on eight successive occasions and the median number of examinations was two. This frequency was somewhat lower than in samples in the general military population.[1] Cultures on blood agar in a number of these cases in which no fungi could be observed did not show streptococci or coagulase-positive

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June 1947.

The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Columbia University. The observations were made at Fort Benning, Ga., through the courtesy of Colonel William R. Denton, Post Surgeon.

1. Hopkins, J. G.; Hillegas, A. B.; Ledin, R. B.; Rebell, G. C., and Camp, E.: Dermatophytosis at an Infantry Post, J. Invest. Dermat. **8**:291 (June) 1947.

staphylococci with significant regularity.[2] The most effective treatment in these cases appeared to be the use of antihidrotics.

### SYMMETRIC LIVIDITIES

A curious type of lesion was seen in many men with, and in a few without, general hyperhidrosis. They presented on pressure areas sharply bordered plaques of white soggy skin surrounded by narrow violet-red borders. The plaques often appeared slightly raised. Little beads of clear fluid appeared on their surface, even when the more normal surrounding skin was fairly dry. The areas were often exquisitely sensitive to touch. They occurred most frequently on the

Fig. 1.—Symmetric lividities in unusual distribution. Plaques were more frequently observed on weight-bearing areas (photograph by United States Army Signal Corps).

sole of the heel and at the heads of the metatarsals, but also on the plantar and lateral surfaces of terminal phalanges and, in fact, anywhere that the shoe or a neighboring toe exerted pressure.

It was generally assumed by the many medical officers who noted these lesions[3] that they were the same as the "symmetric lividities" described by Pernet[4] in 2 children and similar cases reported by Park-

2. Rebell, G. C.: Staphylococci and Hemolytic Streptococci from Normal Skin, and from Cutaneous Infections, J. Invest. Dermat. **8**:13 (Jan.) 1947.

3. (*a*) Nelson, L. M.: Symmetric Lividity of the Soles, Arch. Dermat. & Syph. **47**:822 (June) 1943. (*b*) Park, R. G.: Hyperhidrosis of the Feet, ibid. **48**:538 (Nov.) 1943. (*c*) Kalz, F., and Friedman, H.: Symmetrical Lividity of the Soles, Canad. M. A. J. **51**:252 (Sept.) 1944.

4. Pernet, G.: Symmetrical Lividities of the Soles of the Feet, Brit. J. Dermat. **37**:123 (March) 1925.

hurst[5] and Hitch and Hansen.[6] It should be noted that Pernet and others described the lesions as bluish red and that the name he applied is not descriptive of the disease in our cases, in which the lesions were usually dead white with a narrow cyanotic border. In other respects they seem similar. Although these "lividities" seem rare in civilian practice, they were a frequent and troublesome occurrence among troops in hot climates.

Kalz and Friedman[3c] reported that the sweat from these lividities has a $p_H$ of 4.0 to 5.0, which is more acid than that of normal sweat. Dr. Frederick Kavanagh, who made determinations in 10 of our cases, observed on the contrary, that $p_H$ varied from 6.1 to 7.5, with a median value of 6.5. In measurements from relatively normal areas of the feet in 13 men the $p_H$ range was 4.6 to 6.3, with a median of 5.9. The diminished acidity in the "livid" areas suggests that the exuding droplets contained interstitial fluid or insensible perspiration rather than excretion of the coil glands. In these cases, also, fungi were not seen with significant frequency. In 249 patients examined mycelium was observed in only 33 per cent. Various hypotheses have been advanced as to the causation of these lividities, but all observers have noted their association with hyperhidrosis. Pressure and friction on skin macerated by sweat may be an adequate explanation. Denudation of the horny layer of an edematous area may have permitted exudation of intersititial fluid, which gave the appearance of local sweating.

## TREATMENT

In treatment in these cases, formaldehyde and alum were used in an effort to reduce sweating and tannic acid with the purpose of preventing maceration. Of numerous preparations the following ones seemed most useful:

1. Foot baths containing 4 per cent potassium alum were used in 45 cases of severe diffuse hyperhidrosis, with improvement in about 50 per cent. It seemed the most useful treatment in cases with much inflammation.

2. A 4 per cent solution of formaldehyde painted on the affected areas was used in 76 cases of symmetric lividity. It seemed to give the most prompt relief in this condition. Improvement was recorded in 83 per cent and complete clearing in 33 per cent. It was also used in 172 cases of diffuse hyperhidrosis and was frequently of temporary benefit.

3. For dressing denuded areas, which frequently develop on

5. Parkhurst, H. J.: Symmetrical Lividities of the Soles, Arch. Dermat. & Syph. **27**:663 (April) 1933; Symmetric Erythema of the Soles, ibid. **40**:268 (Aug.) 1939.

6. Hitch, J. M., and Hansen, R. F.: Symmetric Erythema of Soles: "Symmetrical Lividity of Soles of Feet" (Pernet), Arch. Dermat. & Syph. **38**:881 (Dec.) 1938.

hyperhidrotic feet, tannic acid ointments seemed especially useful. The most satisfactory preparations were 10 to 20 per cent tannic acid in a "carbowax" (a polyethylene glycol) base.

4. For prolonged treatment in these cases, powders were more practical and probably of greater benefit. Of various alum powders, one composed of 25 per cent exsiccated potassium alum and 75 per cent talc appeared the most satisfactory. Powders containing 5 per cent paraformaldehyde in talc or bentonite gave more permanent and decisive results in most cases and seem to deserve more trial in the

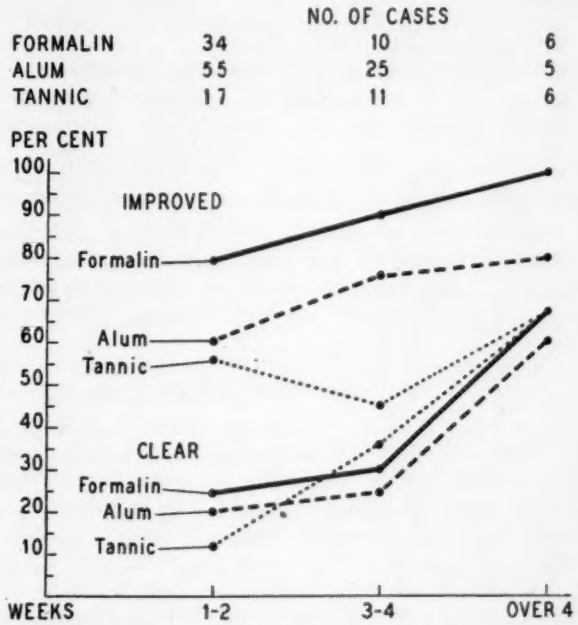



FIG. 2.—Chart comparing results with powders in diffuse hyperhidrosis.

treatment of hyperhidrosis.[7] Powders of from 10 to 20 per cent tannic acid appeared less effective. The value of statistical comparison of our results is suspect, because there is no sharp end point at which one could say that sweating is no longer excessive and records of "improvement" are always unreliable. However, the scores recorded for these three types of powder in cases of diffuse hyperhidrosis are shown in figure 2, and serve to confirm our impression that the paraformaldehyde powder was the most effective of the three.

We were naturally apprehensive about irritation or sensitization from formaldehyde, on account of the known occurrence of occupational dermatitis from its use. However, of 43 patients who used the paraformaldehyde powder only, none showed evidence of dermatitis. In 2 patients fissures developed while they were receiving treatment, which were probably due to excessive drying by the powder. Of 218

patients whose lesions were painted with the 4 per cent solution of formaldehyde, with or without the powder, dermatitis developed in 5 (2.3 per cent), but in no case was it severe or persistent. In 20 of these patients fissures developed while they were receiving treatment. The patients were to some extent selected, as none of the formaldehyde preparations were used for patients already showing signs of eczematization. If used with judgment, we believe that both preparations, especially the paraformaldehyde powder, will prove helpful in the treatment of hyperhidrosis.

## SUMMARY AND CONCLUSIONS

Hyperhidrosis, independent of mycotic or pyogenic infection, was the probable cause of much discomfort and partial disability in troops operating in hot climates.

Symmetric lividities of the soles, which are probably the result of hyperhidrosis plus friction, were of frequent occurrence in such troops.

Paraformaldehyde powder is a therapeutic agent of promise in the treatment of these conditions.

102 East Seventy-Eighth Street.

## ABSTRACT OF DISCUSSION

DR. CORNELIUS FERD LEHMANN, San Antonio, Texas: Because of the fact that every patient with hyperhidrosis does not present symmetric lividity of the soles, it is probable that other factors are contributory.

J. F. Madden (Inflammatory Disorders of Skin of Feet, J. A. M. A. **124**:743 [March 18] 1944) calls attention to the common presence of symmetric lividity of palms and soles in hospitalized patients with tuberculosis. I have noted this occasionally in such patients, who have moist clammy palms and soles. Recently I saw a case of symmetric lividity in a 59 year old man who had Vincent's angina and a toxic rash and who had been walking excessively on the hot pavement.

There is a suggestion that endogenous toxic factors may, by promoting hyperhidrosis, predispose to the condition, particularly in one who, lacking the keratoplastic effect of exercise, naturally has thin-skinned palms and soles.

The use of impermeable shoes and wet socks and excessive standing or walking have been seen as probable precipitating causes. Also the wearing of shoes which are too tightly laced, by creating hemostasis and edema of the soles, is also to be considered as a predisposing cause.

Symmetric lividity in young recruits in their early training period, before their feet and muscles were hardened, was not uncommon. After long hikes their soles appeared bruised. In them, these other factors of impermeable shoes, tightly laced shoes and damp socks appeared as precipitating causes superimposed on the hyperhidrosis which was inherent in them.

All successful types of treatment of symmetric lividity of the soles, which have been reported, have been those which are of help to hyperhidrosis. Therefore, whatever other causative factors are present in the individual case, this is the common denominator in all.

H. J. Parkhurst (Symmetrical Lividities of the Soles, ARCH. DERMAT. & SYPH. **27**:663 [April] 1933) used 25 per cent aluminum chloride successfully; J. M. Hitch and R. F. Hansen (Symmetric Erythema of Soles: Symmetrical Lividities of Soles of Feet [Pernet], ARCH. DERMAT. & SYPH. **38**:881 [Dec.] 1938) used 40 per cent formaldehyde once a week 12 per cent aluminum acetate ointment or 2 per cent aluminum acetate soaks.

L. M. Nelson (Symmetric Lividity of Soles, ARCH. DERMAT. & SYPH. **47**:822 [June] 1943) reported the use of 1 per cent solution of alum, alibour water (water containing zinc and copper sulfates) soaks or 25 per cent solution of aluminum chloride (repeated paintings) to be of little avail, but he got rapid response with 5 per cent powdered alum, 5 per cent tannic acid and 10 per cent boric acid in talcum powder combined with daily soaks in potassium permanganate solution (1 to 5,000).

I have never resorted to anything but either formaldehyde soaks (1 per cent) or aluminum chloride (25 per cent) in daily applications, coupled with good hygiene and reduced activity.

Dr. Hopkins' appraisal of the therapeutic effectiveness of formaldehyde preparations, alum preparations and tannic acid preparations helps one to settle the question of the best treatment for hyperhidrosis and symmetric lividity of the soles.

The paraformaldehyde in powder is promising, since it gives continuous action. One is likelier to get cooperation from a patient in his treatment by using powder than by using soaks. The striking thing about this report is that there were no cases of irritation or hypersensitivity to paraformaldehyde. For the ones who either have hypersensitivity to formaldehyde or irritation from it, one has a choice of alum or tannic acid.

Another application that is of value, because it will tan and constrict the edematous epithelium, is painting daily with saturated solution of potassium permanganate.

DR. RICHARD S. WEISS, St. Louis: I should like to ask whether there has been any experience in the use of lead compounds in these conditions. Years ago Dr. Engman Sr. described the use of plaster of lead oleate in the ointment form. This is made by melting together in a water bath equal parts of plaster of lead oleate and white petrolatum.

This preparation, in my experience, has been almost specific. It is not a cure. It causes the symptoms to disappear; the sogginess and the associated hyperhidrosis disappear; the patient is comfortable and remains so for a period of time and then usually has to repeat the treatment in the next season.

However, I am glad to hear that there is a powder available, and, if it is possible to use the powder after using ointment of lead oleate, it may prove to be preventive also.

DR. ROBERT M. MCKENNA, London England: I saw a relatively small number of cases of symmetric lividity in the British Army. In twelve years' practice before the war, I had scarcely seen a single case in England.

One of the points noticed in the army was that when the patients were admitted to hospital there was lividity around the border of the foot, wheras areas of the sole were soggy and white. The total affected area was the area covered by the rubber of what is called a "gym" shoe. Nevertheless, although every British soldier had a pair of these shoes, my co-workers and I were not able to incriminate the shoes as the cause of the difficulty.

Whereas we were able to alleviate hyperhidrosis of the feet to some extent or stop it temporarily, symmetric lividity of the feet could be cleared up in a fortnight's treatment; the patient was seldom seen again for treatment. We were not

able to follow up the patient properly, but we had the impression that symmetric lividity of the feet was a condition from which a person might suffer one or two attacks, but did not frequently suffer the lividity a third time.

While potassium permanganate was usually satisfactory in treatment, if the men reported for treatment early enough we thought it satisfactory to paint the feet once a week only with a 40 per cent solution of formaldehyde and then use a simple dusting powder containing zinc and boric acid. Sodium hexametaphosphate was sometimes prescribed as an alternative medicament. It is difficult to grind the crystalline form into a powder until it is moistened with alcohol. The compound was usually used as a 10 per cent solution or powder. Some dermatologists found it satisfactory, but many were not satisfied with the results obtained.

DR. JASPER LAMAR CALLAWAY, Durham, N. C.: During the war an opportunity arose for me to examine men working in a precision instrument factory. If their hands tended to sweat, the instruments rusted and they were told to get another job.

Knowing that atropine is cholinergic and will paralyze the sympathetic fibers, I treated them with tincture of belladonna in dosages just short of toxicity. To begin with, the men were given 3 drops of tincture of belladonna daily; the dosage was then increased 1 drop per dose per day, until they began to notice difficulty in visual accommodation or experienced dryness of the roof of the mouth. At that point the dose was decreased about 3 drops, and this lower dosage was maintained, with gratifying results.

I have also used the same type of treatment in a group of young college students, both girls and boys, who had hyperhidrosis not only of the soles of the feet but also of the palms. I observed that dosages just short of the maximum tolerated dose could be maintained in a satisfactory manner for an indefinite period. One of the interesting observations is that many of the patients, after having been given atropine for a period of time, were able to discontinue taking the drug for varying periods, with prolonged relief from hyperhidrosis.

DR. HERBERT S. ALDEN, Atlanta: This condition was a fairly common one among Navy personnel in the Pacific, particularly those persons who had to stand or walk much on the decks of the smaller ships. It sometimes presented a problem.

Rest would invariably relieve the patient, but I found that formaldehyde, almost in any concentration short of producing irritation, was the best and most relieving drug.

Unquestionably, the condition was due either to tight-fitting shoes, shoes that were not comfortable or shoes that had thin soles. The point was brought up in relationship to men in the British Navy. They had shoes with thicker soles, and they seemed to have less trouble.

DR. JOHN G. DOWNING, Boston: I would like to add one more causative factor in regard to these eruptions of the feet and one therapeutic thought. It is the condition which I described in 1942 in a paper presented at the annual meeting of the Massachusetts Medical Society and labeled "painful heels." (Downing, J. G.: Trauma of the Skin Due to Wartime Activities, *New England J. Med.* **227**:539-544 [Oct. 8] 1942). A few years ago I treated a physician, who was to undergo a sympathectomy because of a painful and itching eruption on his feet. On looking inside his shoes I noted that the eruption corresponded to the contact areas where the cement had seeped out around the edge of the heel plate. Having seen similar cases in which I proved that the cement was the causative factor, I was able to avoid the necessity of an operation in this case. I believe that many of the cases described today are due to the same cause. The eruption is usually most apparent at the heels, and the feet hurt usually only when the patient wears shoes. I believe that this was true

with many of the men in service, and a change in the brand of shoes or cement was all that was necessary for relief.

DR. JAMES HERBERT MITCHELL, Chicago: I want to say a word of warning about this free use of formaldehyde. I had my first and worst experience in treating Dr. H. Gillian Wells many years ago.

He had dermatitis due to formaldehyde from which he neyer recovered. His fingers were constantly taped. He was unable to go into a place where there was formaldehyde. It originated when he created the Pathological Museum.

Some time ago I saw a man whose arms were fixed. I think that they could have been embedded in sections without any further fixation. I have seen this repeatedly, and, while formaldehyde can be used, I am sure, in large numbers of troops and naval personnel, I do not rely on its use and I try to get along without using it.

Many of these cases of hyperhidrosis of the palms and soles have a nervous basis, I am sure. I have under observation now a woman who has given up her musical career, because the nervousness incident to an appearance caused so much sweating that she could not play the piano.

DR. H. J. PARKHURST, Toledo, Ohio: I have been interested in symmetric lividities of the soles for many years and have encountered a number oc cases. All the patients presented hyperhidrosis of the soles, but it is obvious that only in an occasional person with hyperhidrosis does lividity develop.

In my experience, the condition has cleared up promptly in all cases following the application of a 25 per cent solution of aluminum chloride. There has been a tendency toward recurrence when the astringent was discontinued.

I have not observed that perspiration occurred only in the erythematous patches. It has always seemed to be diffuse. There may be a neurocirculatory factor, and some local infection may play a part in the causation. Further investigation is required.

DR. MARION B. SULZBERGER, New York: Hyperhidrosis of the palms and soles is an everyday problem not only in military medicine but in civilian life and practice. In the localized form of hyperhidrosis, there is often and undoubtedly a nervous mechanism at play.

There is a recent article by Dr. S. Feinberg which mentions the use of the antihistaminic agents, such as "pyribenzamine hydrochloride" N. N. R. (tripelennamine hydrochloride), as being effective in hyperhidrosis of the hands and feet.

Have any of the members had any experience with this drug in treating patients for hyperhidrosis?

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: Symmetric lividity of the feet is an interesting disease. It is like no other disease. It is not particularly well named, but I have no better name for it. It is not invariably symmetric. Often it affects the toes as well as the heels and seems not necessarily to be concerned with contact agents. It is a "little" disease, but a significant one in some circumstances, particularly to the man who has it. In addition to the pain, there is its strong odor.

It is not related to the hyperhidrosis of anxiety neuroses and psychoneuroses. The patients do not necessarily have wet palms and soles.

In the cases I handled in my military career, I observed that salicylic acid and sulfur salve with a petrolatum base was more effective than a powder preparation.

Roentgen ray therapy is effective. A single dose of 150 r may be effective. Of course, this is a measure that interferes with sweating.

---

7. Dr. Gustav J. Martin of the United Drug Co., Philadelphia, suggested the use of paraformaldehyde and supplied the powders.

# GRANULOMA INGUINALE

## A Review of the Literature and a Report of Ninety-Seven Cases, With a Note on Streptomycin Therapy

LYDIA MARSHAK, M.D.
CHICAGO

ROBERT L. BARTON, M.D.
DUBUQUE, IOWA

AND

THEODORE J. BAUER, M.D.
Senior Surgeon, United States Public Health Service
CHICAGO

THE LARGE shifts of population which accompanied the recent war created a hitherto unprecedented number of cases of granuloma in the North. Thus, in the space of three years, in the city of Chicago, where the disease was a relative rarity, almost 100 patients were seen and treated at the Chicago Intensive Treatment Center. It appears timely, in view of the large increase in the number of cases seen in northern cities recently, to review the literature on this disease, with particular attention to the newer methods of treatment.

McLeod[1] in India first described the disease as a "serpiginous ulceration of the genitals," and Conyers and Daniels[2] in 1896 first recognized the disease as a distinct clinical entity. In 1905 Donovan[3] in India demonstrated the organism which today bears his name. In 1913 Aragao and Vianna[4] introduced antimony potassium tartrate in the treatment of the disease.

---

Under the direction of Herman N. Bundesen, Senior Surgeon (R), United States Public Health Service (Inactive), President, Chicago Board of Health.

From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health, in cooperation with the United States Public Health Service.

1. McLeod, K.: Precis of Operations Performed in the Wards of the First Surgeon Medical College Hospital During the Year 1881, Indian M. Gaz. **17**:120, 1882.

2. Conyers, J. K., and Daniels, C. W.: Lupoid Form of the S-Called Groin Ulcerations, British Guiana M. Ann. **8**:13, 1896.

3. Donovan, C.: Medical Cases from Madras General Hospital, Indian M. Gaz. **40**:414 (Nov.) 1905.

4. Aragao, U. de B., and Vianna, J.: Pesquizas sobre o granulome venero, Mem. Inst. Oswaldo Cruz **11**:211, 1913.

In 1915 the first cases seen in the United States were reported by Grindon,[5] and in 1921 Campbell[6] pointed out that the disease was not uncommon in this country. Numerous cases of granuloma inguinale were subsequently reported in different areas of the United States, by Randall, Small and Belk[7] in Philadelphia, Gage[8] in New Orleans, Shattuck[9] in Boston, Fox[10] in New York and a number of others.[11] Excellent reviews have been published by D'Aunoy and Von Haam,[12] Harris,[13] Pariser and Beerman[14] and Robinson and his co-workers.[15]

Although extragenital lesions had been described by Donovan,[3] Harris[13] and others, the disease was considered to be peculiarly localized to the perineal region. Greenblatt and his co-workers[16] reported additional extragenital lesions. They also described the "pseudobubo," in which periadenitis exists in association with subcutaneous lesions of granuloma inguinale. Despite the absence of true adenitis, the Donovan bodies were observed by these authors repeatedly in the regional lymph nodes and in the regional lymphatic vessels. Lymphangitic abscesses, so-called bubonuli, caused by granuloma ingui-

5. Grindon, J.: Granuloma Inguinale Tropicum, Arch. Dermat. & Syph. **31**:236 (March) 1913.

6. Campbell, M. F.: Granuloma Inguinale, J. A. M. A. **76**:648 (March) 1921.

7. Randall, A.; Small, J. C., and Belk, W P.: Tropical Inguinal Granuloma in Eastern U. S., J. Urol. **5**:539 (June) 1921. Randall, A., and Small, J. C.: Granuloma Inguinale, Surg., Gynec. & Obst. **34**:717 (June) 1922.

8. Gage, I. M.: Granuloma Inguinale, Arch. Dermat. & Syph. **7**:303 (March) 1923.

9. Shattuck, G. C.: Granuloma Inguinale in Boston, Boston M. & S. J. **188**:530 (April 12) 1923.

10. Fox, H.: Granuloma Inguinale: Its Occurrence in the U. S.; a Report of Fifteen Cases Observed in New York, J.A.M.A. **87**:1785 (Nov. 27) 1926.

11. Briggs, P. R.: Granuloma Inguinale, New England J. of Med. **212**:330 (Feb. 21) 1935. Brandt, R., and Gatewood, T. S.: Early Diagnosis of Granuloma Inguinale, Am. J. Syph., Gonor. & Ven. Dis. **25**:48 (Jan.) 1941. Symmers, D.: Granuloma Inguinale in the United States, J. A. M. A. **74**:1304 (May 8) 1920. McIntosh, J. A.: The Etiology of Granuloma Inguinale, ibid. **87**:996 (Sept. 25) 1926.

12. D'Aunoy, R., and Von Haam, E.: Granuloma Inguinale, Am. J. Trop. Med. **17**:747 (Sept.) 1937.

13. Harris, R.: Granuloma Venereum, Laryngoscope **40**:707 (Oct.) 1930.

14. Pariser, H., and Beerman, H.: Granuloma Inguinale, Am. J. M. Sc. **208**:547 (Oct.) 1944.

15. Robinson, H. M.; Robinson, H. M., Jr.; Shelley, H. S., and Mays, H. B.: The Treatment of Granuloma Inguinale, South. M. J. **35**:889 (Oct.) 1942.

16. Greenblatt, R. B.; Dienst, R. B.; Pund, E. R., and Torpin, R.: Experimental and Clinical Granuloma Inguinale, J. A. M. A. **113**:1109 (Sept. 16) 1939. Greenblatt, R. B.; Torpin, R., and Pund, E. R.: Extragenital Granuloma Inguinale, Arch. Dermat. & Syph. **38**:358 (Sept.) 1938.

nale, were described by Sobel and Pensky.[17] Arnell and Potekin[18] reported 38 cases in which the disease attacked the cervix uteri. The seriousness of the prognosis of the disease, particularly when lesions of the cervix coexisted with pregnancy, was brought out in a report by Pund and McInnes,[19] who observed 6 fatal cases of the disease.

It is far from being a strictly localized disease; Lyford and his associates[20] in 1944 and Sheldon[21] in 1945 pointed out that polyarticular arthritis and osteomyelitis are not uncommon in granuloma inguinale. Lyford's patient died of disseminated granuloma inguinale with miliary bone and joint involvement. Metastatic lesions in bones and skin, with severe constitutional symptoms, were discovered in a patient observed by Paggi and Hull,[22] and Becker[23] reported a case of a patient who at autopsy presented lesions of granuloma inguinale in the intestinal tract and ribs.

Despite the fact that the disease has been recognized clinically for over half a century, there was considerable doubt regarding the causative agent of the disease. Recent work by Anderson, deMonbreun and Goodpasture[24] has done much to clarify the nature of the infecting organism. They were successful in culturing the causative agent of granuloma inguinale in the egg yolk of developing chick embryos. The isolated micro-organisms observed by them in continuous serial cultures were observed to be morphologically identical with the Donovan bodies taken from lesions and to represent a gram-negative bipolar

17. Sobel, N., and Pensky, N.: Bubonulus in Granuloma Inguinale, Arch. Dermat. & Syph. **48**:494 (Nov.) 1943.

18. Arnell, R., and Potekin, J.: Granuloma Inguinale of the Cervix: Thirty-Eight Cases, Am. J. Obst. & Gynec. **39**:626 (April) 1940.

19. Pund, E. R., and McInnes, G. F.: Granuloma Venereum: A Cause of Death; Report of Six Fatal Cases, Clinics **3**:211 (June) 1944.

20. Lyford, J.; Scott, R. B., and Johnson, R. W., Jr.: Polyarticular Arthritis and Osteomyelitis Due to Granuloma Inguinale, Am. J. Syph., Gonor. & Ven. Dis. **28**:588 (Sept.) 1944. Scott, R. B.; Lyford, J., and Johnson, R.: Granuloma Inguinale as a Cause of Arthritis and Osteomyelitis, Bull. Johns Hopkins Hosp. **74**:213 (March) 1944. Lyford, J.; Johnson, R.; Blackman, S., and Scott, R.: Pathological Findings in a Case of Granuloma Inguinale with Milliary Bone and Joint Involvement. ibid. **79**:349 (Nov.) 1946.

21. Sheldon, W. H., and others: Osteomyelitis Caused by Granuloma Inguinale, Am. J. M. Sc. **210**:237 (Aug.) 1945.

22. Paggi, L. C., and Hull, E.: Metastatic Granuloma Venereum, Ann. Int. Med. **20**:686 (April) 1944.

23. Becker, S. W., in discussion on Greenblatt, Dienst, Pund and Torpin.[16]

24. Anderson, K.; deMonbreun, W. A., and Goodpasture, E. W.: An Experimental Investigation of the Etiology and Immunology of Granuloma Inguinale, Am. J. Syph., Gonor. & Ven. Dis. **2**:165 (March) 1945. Anderson, K., and others: An Etiologic Consideration of Donovania Granulomatis, J. Exper. Med. **81**:25 (Jan.) 1945.

(safety-pin-like) bacillus which multiplies in characteristic encapsulated form. For this organism they proposed the name of "Donovania granulomatis."

## REVIEW OF CASES OBSERVED AT THE CHICAGO INTENSIVE TREATMENT CENTER

From October 1943 through November 1946, 97 patients with granuloma inguinale were observed. Fifty of these were male and 47 female. (Greenblatt[25] reported that of 75 cases observed at the University of Georgia in eight years, granuloma inguinale was diagnosed in only 3 white patients.) All but 1 were Negro. In 79 patients the diagnosis was confirmed by the presence of Donovan bodies in smears taken from the lesions. In the 18 patients in whom Donovan bodies could not be demonstrated, the diagnosis rested on the clinical appearance of the lesions, histologic studies of biopsy specimens obtained[26] and the response to treatment with antimony drugs. The youngest patient was 16 and the oldest 54. The patients fell into the following age groups:

| | |
|---|---|
| 16 to 25 yr. | 53 patients |
| 25 to 35 yr. | 29 patients |
| 35 to 45 yr. | 10 patients |
| 45 to 54 yr. | 5 patients |

The lesions of the male patients were observed in the following locations:

| | |
|---|---|
| Glans, corona and prepuce | 34 cases |
| Perineum, perianal region, scrotum, thighs | 5 cases |
| Perianal region only | 3 cases |
| Inguinal folds involved | 9 cases |

It is of interest to note that in 3 homosexual male patients the lesions were limited exclusively to the anal region, a fact which lends weight to the venereal nature of granuloma inguinale.

That the location about the anus may lead to serious complications was shown by Crane and Kimball[27] in their report of a case of granuloma inguinale involving the rectum and the colon, complicated by fever, rectal bleeding, severe anemia and strictures. Goldberg[28] and Berkowitz[29] described lesions about the anus and stressed

25. Greenblatt, R. B.: Management of Chancroid, Granuloma Inguinale and Lymphogranuloma Venereum in General Practice, Ven. Dis. Inform., 1943, Supp. 19.

26. These were done by Dr. Marcus Rayner Caro, Clinical Associate Professor of Dermatology, University of Illinois.

27. Crane, W., and Kimball, H. S.: Granuloma Venereum, Involving the Rectum and Colon, California & West. Med. **52**:177 (April) 1940.

28. Goldberg, L. C.: Treatment of Granuloma Inguinale with Anthiomaline: Report of a Case with Extragenital Lesion, Am. J. Syph., Gonor. & Ven. Dis. **29**:608 (Nov.) 1945.

29. Berkowitz, J.: Granuloma Inguinale: A Proctologic Consideration, New England J. Med. **234**:625 (May 9) 1946.

the importance of searching for Donovan bodies in lesions limited to the region about the anus, which can be mistaken for anorectal fissures, syphilitic lesions or malignant growths.

In the female patients seen, the lesions were distributed as follows:

| | |
|---|---|
| Fourchet, labia | 32 cases |
| Clitoris and vaginal walls | 3 cases |
| Perineum, inner aspect of thighs and perianal region | 8 cases |
| Inguinal folds | 8 cases |
| Vulvectomy scars | 2 cases |

The duration of the disease varied from one week to more than fourteen years. In 34 of the patients there was no coexistent disease, but in the remainder the following diseases were observed in association with granuloma inguinale:

| | |
|---|---|
| Latent syphilis | 20 cases |
| Neurosyphilis (asymptomatic) | 6 cases |
| Lymphogranuloma venereum | 2 cases |
| Gonorrhea | 6 cases |
| Chancroid | 7 cases |
| Chancroid, early latent syphilis and gonorrhea | 10 cases |
| Dark field positive primary or secondary syphilis | 12 cases |

Allison,[30] in a recent report of 200 cases of granuloma inguinale from Georgia, stated that he had observed 3 deaths, primarily due to severe anemia and cachexia. While no fatal cases were observed in this series, the debilitating anemia seen in this disease was noted. The following tabulation reveals the diminution of the hemoglobin in the patients in our series:

| | |
|---|---|
| 6 to 8 Gm. hemoglobin | 3 cases |
| 8 to 10 Gm. hemoglobin | 11 cases |
| 10 to 12 Gm. hemoglobin | 24 cases |
| 12 to 14 Gm. hemoglobin | 22 cases |

In general, the longer the duration of the disease, the lower was the hemoglobin estimation. The 3 patients in whom the hemoglobin ranged from 6 to 8 Gm. had suffered from the disease for from ten to fourteen years.

Patients seen early in this study were treated on an outpatient schedule, and, unfortunately, many of these discontinued their visits before a significant amount of treatment could be administered. Because of the irregularity of treatment and because of the poor treatment results which were obtained by the outpatient schedule of treatment, all patients seen with the disease from March 1946 to November 1946 were hospitalized, so that treatment could be completely controlled. By this means and with a 1 per cent solution of antimony potassium tartrate given intravenously, there was a gratifying response in even the old neglected cases. The dose of the drug ranged from 1 to 10 cc., in ascending doses of 1 cc. per day gradually, and after the maximal dose was reached a decreasing dose, by 1 cc. per day, was administered for the next ten days. A course of treatment was considered a total of 100 cc. of antimony potassium tartrate. Twenty-one

30. Allison, G. G.: Granuloma Inguinale: A Study of Two Hundred Cases, J. M. A. Georgia **35**:103 (April) 1946.

of the 25 patients thus treated exhibited complete healing at the end of the full course of treatment (100 cc. of antimony potassium tartrate). Two additional patients required two complete courses of the drug for satisfactory results. Two patients did not respond to antimony potassium tartrate.

Rather severe nausea, vomiting and aching pains were occasionally observed when the larger dose of antimony potassium tartrate (8 to 10 cc.) was employed. In no case was it necessary to discontinue completely the antimony therapy, but the dosage had to be reduced and treatments were given at longer intervals, which considerably delayed the healing of the lesions. It was our experience that freshly prepared 1 per cent solution of antimony potassium tartrate administered intravenously was superior to either "anthiomaline" (lithium antimony [trivalent] thiomalate prepared as a 6 per cent solution, 1 cc. of which contains about 0.01 Gm. of antimony) or stibophen ("fuadin").

A recent report[31] on the use of resin in podophyllum for lesions of granuloma inguinale led us to treat 6 patients with resin of podophyllum (25 per cent suspension in liquid petrolatum). In 4 of these patients a remarkably beneficial response to treatment was observed, but in 2 patients the local reaction to resin of podophyllum was so severe as to preclude our using this drug routinely.

In 5 of the 46 (10.7 per cent) patients treated and observed regularly, the use of antimony drugs was completely unavailing.[32] For 1 of these patients with antimony-resistant disease, the report of whose case follows, streptomycin was employed with brilliant results.

## REPORT OF CASES

CASE 1.—W. G., a 33 year old Negro woman, was first admitted to the center on June 28, 1943, with destructive lesions of the right labium majus and posterior aspect of the fourchet associated with edema of the vulva. The reaction to the Kahn serologic test for syphilis was positive (20 units) and a dark field examination of the serum from one of the lesions on the labium majus yielded positive results for Treponema pallidum. A diagnosis of seropositive primary syphilis was made. Intensive treatment consisting of eight hours of induced fever at a level of 106 F. (rectal); 96 mg. of oxophenarsine hydrochloride and 150 mg. of bismuth compound were administered concurrently in twenty-four hours. In addition, 2 Gm. of sulfathiazole every four hours for five days was given to clear up the secondary infection. The lesions improved considerably, and the patient was dismissed on July 13. When the patient was seen in the outpatient department in September 1944, the lesions

31. Tomskey, G. C., and Vickery, C. W.: Successful Treatment of Granuloma Inguinale with Special Reference to the Use of Podophyllin, J. Urol. **48**:401 (Oct.) 1942.

32. Robinson and his co-workers[15] observed 30.2 per cent failures in their series of 46 patients treated with antimony drugs.

were healed, but in the early part of 1944 new lesions developed and the patient was readmitted in October. On admission, large red granulomatous ulcerations occupied the lower third of the labia majora and minora and the fourchet. At this time the results of both the Kahn serologic test for syphilis and the dark field examination were negative. The leukocyte count was 6,100 cells per cubic millimeter, and the hemoglobin was 12.2 Gm. per hundred cubic centimeters of blood. Urinalysis revealed no abnormalities. Gonococci could not be seen in cervical and urethral cultures. Numerous Donovan bodies were demonstrated in spreads from the lesions. Treatment with stibophen (5 cc. every three days) was started on October 13, and the patient was dismissed on October 26, further treatment to be given in the outpatient department. From October 26, 1944, to January 1947, she

Fig. 1 (case 1).—Appearance of the lesions before treatment with streptomycin.

was given various antimony preparation, one to three times a week, practically without interruption. During this period of time she received a total of three and one-half courses of stibophen (245 cc.), one course of "anthiomaline" (60 cc.) and two courses of antimony potassium tartrate (202 cc.) There was temporary improvement, but the lesions never healed completely and there were periods of definite progression in size. Antimony potassium tartrate was not well tolerated and had to be given in smaller doses. The patient experienced a severe reaction to the local use of resin of podophyllum. The general impression was that the lesions had responded poorly to each of the antimony preparations given, although there had been, at times, a transient tendency toward healing.

The patient was readmitted to the hospital on January 28. There were extensive moist papilliform vegetations about the labia majora and flat dry scarred areas on the fourchet and vaginal walls. (fig. 1). A profuse, foul-smelling discharge was present. The reaction to the serologic test for syphillis was negative. The hemoglobin was reported at 12.3 Gm. per hundred cubic centimeters of blood. The white blood cell count was 7,000 per cubic millimeter. Donovan bodies were present in the scrapings from the lesions. Streptomycin therapy was begun on January 29. She received 50,000 units every three hours until February 25, or a total of 10,250,000 units.

There was continuous progressive improvement, dating from the first day of treatment. Donovan bodies could not be demonstrated in smears from lesions made

Fig. 2 (case 1).—After treatment with streptomycin the vulva was more nearly normal in appearance, with all lesions epithelized.

on February 6, the ninth day of treatment, and thereafter. At the end of treatment, the vulva was more nearly normal in appearance, with all lesions epithelized (fig. 2). The papillomatous vegetations had completely disappeared and were replaced by scar tissue. When next seen, on April 26, no lesions were present.

Another patient, not previously treated for granuloma inguinale, showed an equally prompt response to streptomycin therapy. The report on this case is as follows:

Case 2.—J. R., a 27 year old Negro woman, was referred to the center on Aug. 25, 1946, by one of the clinics for venereal disease. Past history revealed that a

diagnosis of "elephantiasis of the labia of gonorrheal origin" and late latent syphilis was made at that clinic in October 1943, when three injections of an arsenical were given. In March 1945 she was admitted to a hospital in the city for the same condition, where she was given sulfathiazole tablets orally and wet potassium permanganate compressed to the vulva.

On admission to the center, the patient stated that the same vulvar lesions had been present continuously since 1943. Examination revealed a well developed Negro woman. The only abnormal observations were the grotesquely enlarged (about twice normal size) genitalia. There was woody edema of the labia majora. Extensive red granulomatous lesions occupied the greater part of the vulva and both inguinal folds, the clitoris, part of the adjoining vaginal wall and the pubis. The area about the anus was covered with soft moist "beefy" ulcers. The borders of the lesions presented a pearly rolled appearance.

Studies of the blood revealed the hemoglobin to be 8.6 Gm. per hundred cubic centimeters of blood and 3,000,000 erythrocytes and 6,400 leukocytes per cubic millimeter, with 66 per cent filaments, 32 per cent lymphocytes and 2 per cent monocytes. The urine was normal. No gonococci could be demonstrated by culture. The reaction to the Kahn serologic test for syphilis was negative. Dark field examination revealed no T. pallidum, but Donovan bodies were demonstrated in stained scrapings of the lesions.

Streptomycin therapy was begun on Sept. 5, 1946, consisting of 50,000 units every three hours, or a total of 6,175,000 units. After the sixteenth day, on September 21, treatment was discontinued because of the exhaustion of our supply of streptomycin.

Definite improvement could be seen after the first week of treatment, on September 12. There was less moisture in the lesions; the borders appeared flatter, and there was distinct epithelization at the periphery. Donovan bodies could no longer be demonstrated in scrapings from lesions on September 12. Continuous healing was noted from day to day after streptomycin injections had been discontinued. When the patient was dismissed from the center, on October 7, all lesions were epithelized and the edema of the labia was considerably reduced.

The patient was again seen on April 8, 1947, seven months after treatment. There were smooth depigmented scars replacing all the previous lesions; the skin of the labia majora appeared wrinkled, because of the disappearance of the edema.

## COMMENT

Streptomycin, in our opinion, is an effective therapeutic agent in the treatment of granuloma inguinale. The results presented in this paper and the results in the 3 patients whose cases were previously reported[33] from this hospital convincingly demonstrate the efficacy of the drug in this disease. The small dosage of streptomycin employed in the patients treated in this series was effective in healing the lesions. Inasmuch as the tendency to relapse is a notorious feature of granuloma inguinale, time alone will tell whether or not the patients were cured. Greater experience with the drug will be needed before any conclusion regarding the time-dose relationship can be

33. Barton, R. L.; Craig, R. M.; Schwemlein, G. X., and Bauer, T. J.: Granuloma Inguinale Treated with Streptomycin: Report of Three Cases, to be published.

established. It is significant, however, that, with the aforementioned relatively small doses of the drug, none of the symptoms of intolerance described by Brown and Hinshaw and by others[34] were noted.

## CONCLUSIONS

1. Granuloma inguinale is appearing with increasing frequency in the northern states.

2. When patients with granuloma inguinale are hospitalized and given regular treatment, freshly prepared 1 per cent solution of antimony potassium tartrate is an effective agent in the treatment of the disease.

3. In 1 patient not previously treated and in another patient treated unsuccessfully with antimony salts, streptomycin was observed to be of outstanding value in the healing of the lesions.

---

34. Brown, H. A., and Hindshaw, H. C.: Toxic Reaction of Streptomycin on the Eighth Nerve Apparatus, Proc. Staff Meet., Mayo Clin. **21**:347 (Sept. 4) 1946. Fowler, E. P., and Seligman, E.: Otic Complications of Streptomycin Therapy: A Preliminary Report, J. A. M. A. **133**:87 (Jan. 11) 1947. Hettig, R. A., and Adcock, J. D.: Studies of the Toxicity of Streptomycin for Man, Proc. Am. Federation Clin. Research **2**:68, 1945.

# SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

## Effect of Quinacrine Hydrochloride on the Incidence of Convulsions

CAPTAIN WILLIAM J. WELCH
Medical Corps, Army of the United States

ELI BAUMAN, M.D.
NEW YORK

CAPTAIN PETER KNOWLTON
Medical Corps, Army of the United States

AND

ROBERT W. BERLINER, M.D.
NEW YORK

THE EFFICACY of quinacrine hydrochloride ("atabrine") in the suppression and treatment of malaria has been demonstrated unequivocally by the experience in both civilian laboratories and the armed forces in recent years. The qualities which make it preferable to quinine as an antimalarial agent are now well recognized,[1] and it seems certain that it will be used widely in the future. For the latter reason, a note of caution is warranted concerning the use of quinacrine hydrochloride in the termination of therapeutic malaria in patients with dementia paralytica.

Toxic psychoses have been previously described as occurring in patients receiving therapeutic doses of quinacrine hydrochloride for clinical malaria, more particularly when medication is administered parenterally.[2] However, the incidence of this phenomenon is low in otherwise normal persons.

---

From the Department of Medicine, New York University College of Medicine, and the Research Service, Third (New York University) Medical Division, Coldwater Memorial Hospital, New York.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York University.

A portion of this work was presented at the meetings of the Federation of American Societies for Experimental Biology, March 1946 (Welch, W. J.: Knowlton, P.; Bigelow, F. S.; Bauman, E., and Berliner, R. W.: The Incidence of Convulsions in General Paretics Receiving Quinacrine, Federation Proc. **5**:213-214 (March) 1946).

1. Quinacrine Hydrochloride (Atabrine) for Malaria, Board for the Coordination of Malarial Studies, J. A. M. A. **125**:977 (Aug. 5) 1944.

2. Kingsbury, A. N.: Psychoses in Cases of Malaria Following Exhibition of Atabrine, Lancet. **2**:979, 1934. Gaskill, H. S., and Fitz-Hugh, T., Jr.: Toxic Psychoses Following Atabrine, Bull. U. S. Army M. Dept., 1945 no. 86, p. 63. Lidz, T.,

Convulsive seizures are not infrequent in experiments with animals receiving toxic doses of quinacrine hydrochloride. However, their occurrence during the administration of the usual therapeutic doses to human beings has been infrequent. This does not appear to be the case when similar doses of quinacrine hydrochloride are administered to patients with advanced syphilis of the central nervous system for the termination of therapeutic malaria. The occurrence of convulsive seizures in this situation is the subject of the present report.

## MATERIAL

The data are derived from a study of 268 male patients with dementia paralytica with induced malaria at the Manhattan State Hospital during a two year period and 150 patients drawn at random from a larger series of patients with neurosyphilis with induced malaria at the Goldwater Memorial Hospital.

*Manhattan State Hospital.*—The patients observed at the Manhattan State Hospital were in states of mental and physical deterioration sufficiently advanced to have led to their commitment to a state mental hospital. One hundred and fifteen of the 268 patients received quinacrine hydrochloride for the termination of therapeutic malaria, while the remaining 153 received quinine.

Of the patients treated with quinacrine hydrochloride, 23 received relatively small doses (0.4 to 1.0 Gm. in four to six days), while 114 received full therapeutic doses (2.8 to 3.1 Gm. in six to eight days). Twenty-two patients received both large and small doses in separate courses of quinacrine hydrochloride therapy. The period of time during which each patient is exposed to the effects of quinacrine is prolonged well beyond the period of actual administration of the drug, because of the persistence of quinacrine in the body.[3] Consequently, in estimating the period of exposure of each patient to quinacrine, it has seemed advisable to place the duration of the quinacrine risk at eight days in the case of smaller doses and twelve days in the case of larger doses. Thus calculated, the total period during which significant concentrations of quinacrine in the plasma were maintained comprises 1,336 patient-days. The same patients were observed for a total of 10,480 patient-days, during which they received no quinacrine hydrochloride.

The patients who received quinine were given full therapeutic doses (2 Gm. daily for five to eight days). Quinine disappears rapidly

and Kahn, R. L.: Toxicity of Quinacrine (Atabrine) for the Central Nervous System, Arch. Neurol. & Psychiat. **56**:284 (Sept.) 1946.

3. Shannon, J. A.; Earle, D. P., Jr.; Brodie, B. B.; Taggart, J. V.; Berliner, R. W., and others: The Pharmacological Basis for the Rational Use of Atabrine in the Treatment of Malaria, J. Pharmacol. & Exper. Therap. **81**:307, 1944.

from the body when administration of the drug is stopped; consequently, only the period of actual drug therapy is considered in calculating the time during which each patient was exposed to the effects of quinine. So calculated, the total period for the patients treated with quinine consitutes 1,040 patient-days. The same persons were observed for 13,033 patient-days, during which time they received no medication.

*Goldwater Memorial Hospital.*—The patients observed at the Goldwater Memorial Hospital were generally characterized by lesser degrees of organic damage to the brain, many being completely free of signs or symptoms of neurosyphilis. These patients were referred for treatment by department of health clinics and, on completion of fever therapy, were returned to the community and to their usual employment. Only patients who received quinacrine hydrochloride have been selected for inclusion in this analysis. The patients at Goldwater Memorial Hospital received the same dosage of hydrochloride quinacrine as the patients at Manhattan State Hospital, and the period of exposure to the drug, calculated in the same way as for the latter, totaled 1,940 patient-days.

## RESULTS

Convulsions in the course of dementia paralytica, whether occurring spontaneously or precipitated by quinacrine, are frequently multiple. One patient suffered as many as fifteen discrete seizures in a single day. Repeated seizures of this type have not been tabulated separately. Rather, all convulsive seizures occurring in a single patient within a period of two to three days are considered to represent a single convulsive episode.

Periods of acute confusion or mania that occurred during the administration of quinacrine hydrochloride have been omitted from consideration, since they are difficult to distinguish from similar episodes occurring in the natural course of dementia paralytica.

The incidence of convulsive episodes in the various groups studied is given in the table. Two of the patients treated at Goldwater Memorial Hospital had convulsions during a total of 1,940 patient-days of treatment with quinacrine hydrochloride, a rate of one and three-hundredths convulsive episodes per thousand patient-days. No convulsions occurred during the period when no drug was being administered.

The incidence of convulsive episodes in all the patients observed at Manhattan State Hospital during the control periods was one and twenty-eight hundredths per thousand patient-days. During the control period the rate for the group which received quinacrine hydrochloride (one and fourteen hundredths) does not differ significantly

from the rate for the group which received quinine (one and thirty-one hundredths). Likewise, the incidence of convulsions during quinine therapy (one and ninety-two hundredths) was not significantly different from that of the controls. The incidence of convulsions among the patients receiving quinacrine hydrochloride was fourteen and two-tenths per thousand patient-days. This rate represents more than a tenfold increase over either of the control groups. The statistical aspect of this difference is significant.

The nineteen convulsive episodes occurred between the first and seventh days of medication with quinacrine hydrochloride, fifteen falling between the third and sixth days. None of the episodes began after actual administration of the drug was discontinued. Since exposure to the effects of quinacrine has been considered as extending

*Incidence of Convulsions in Patients with Syphilis of the Central Nervous System Receiving Quinine and Quinacrine Hydrochloride*

| Series | Medicament | Period | Nupmber of Patients | Duration of Observation (Patient-Days) | Number of Convulsive Episodes | Incidence of Convulsive Episodes per 1,000 Patient-Days |
|---|---|---|---|---|---|---|
| Manhattan State Hospital | Quinine | During control period | 153 | 13,033 | 17 | 1.31 |
| | | While receiving quinine | 153 | 1,040 | 2 | 1.92 |
| | Quinacrine hydrochloride | During control period | 115 | 10,480 | 12 | 1.14 |
| | | While receiving quinacrine hydrochloride | 115 | 1,336 | 19 | 14.2 |
| Goldwater Memorial Hospital | Quinacrine hydrochloride | During control period | 150 | 8,482 | 0 | 0 |
| | | While receiving quinacrine hydrochloride | 150 | 1,940 | 2 | 1.03 |

beyond the time when medication was stopped, the figure for the incidence of convulsions during treatment with quinacrine hydrochloride would be increased by approximately 50 per cent if calculated only for the period when quinacrine hydrochloride was being administered.

Concentrations of quinacrine hydrochloride in the plasma were determined[4] on or close to the day of convulsion in 11 cases. The level of quinacrine in the plasma exceeded 75 mg. per liter in 9 cases; the lowest concentration in the plasma associated with a convulsive episode was 23 mg. per liter. However, the range of plasma levels among patients in whom convulsions developed does not differ from

4. Brodie, B. B., and Udenfriend, S.: The Estimation of Atabrine in Biological Fluids and Tissues, J. Biol. Chem. **151**:299, 1943.

that observed in patients in whom there was no evidence of cerebral toxicity while they were receiving quinacrine hydrochloride.

## COMMENT

Convulsions are not an unusual occurrence in the course of dementia paralytica. However, the incidence is greatly augmented during the administration of quinacrine hydrochloride in the usual therapeutic doses. The importance of the severity of preexisting organic cerebral damage in producing such a result is shown by the strikingly lower rate in the patients who were closer to being normal who were receiving quinacrine hydrochloride at Goldwater Memorial Hospital. The data do not indicate that, in the usual therapeutic doses, quinine is a factor in the precipitation of convulsive seizures in this type of patient. Consequently, it would appear that, of the two antimalarial drugs in general use, quinine is the drug of choice for the termination of induced malaria in patients with dementia paralytica. It is to be emphasized that this does not obtain for the suppression and treatment of malaria in the otherwise normal person.

## SUMMARY AND CONCLUSIONS

In a series of 115 patients with dementia paralytica who received quinacrine hydrochloride for the treatment of induced malaria, nineteen convulsive episodes occurred during 1,336 patient-days, an incidence of fourteen and two-tenths convulsions per thousand patient-days of treatment with quinacrine hydrochloride as compared with twelve episodes in 10,480 patient-days, or an incidence of one and fourteen hundredths convulsions per thousand patient-days when quinacrine hydrochloride was not administered.

In a group of 153 patients with dementia paralytica who were given quinine for induced malaria, there were two convulsions in 1,040 patient-days, an incidence of one and ninety-two hundredths convulsive episodes per thousand patient-days of treatment with quinine, as compared with seventeen episodes in 13,033 patient-days or a rate of one and thirty-one hundredths convulsions per thousand patient-days when no medication was given.

In a series of 150 patients with neurosyphilis, but with lesser degrees of organic deterioration, there were no convulsions during the control observation period and two during 1,940 days of treatment with quinacrine hydrochloride, a rate of one and three hundredths convulsions per thousand patient-days.

The existence of organic lesions of neurosyphilis predisposes to convulsions when quinacrine hydrochloride is administered. Consequently, in the termination of induced malaria in patients with dementia paralytica, the use of quinacrine hydrochloride should be avoided.

# SYSTEMIC RETICULOENDOTHELIAL GRANULOMA

## Comparison of Letterer-Siwe Disease, Schueller-Christian Disease and Eosinophilic Granuloma

CARL W. LAYMON, M.D.
AND
JOHN J. SEVENANTS, M.D.
MINNEAPOLIS

SYSTEMIC reticuloendothelial granuloma is the generic term used by Wallgren[1] in 1940 to include Letterer-Siwe disease and Schüller-Christian disease. During the past two decades there have been numerous articles devoted to this subject, largely by pathologists, pediatrists, internists and orthopedists. Dermatologists, however, have apparently paid little attention to the cutaneous manifestations of systemic reticuloendothelial granuloma, judging from the paucity of articles which have appeared in dermatologic journals. In articles written within the past few years, Farber,[2] Mallory[3] and Jaffe and Lichtenstein[4] also included eosinophilic granuloma of bone in the group of systemic reticuloendothelial granulomas. The following classification was proposed by Mallory:[3]

1. The disease may mainfest itself in infancy or early childhood in a rapidly fatal form in which the lesions are widely distributed both through the soft tissues (especially the lymphoid tissues) and the skeleton (so-called Letterer-Siwe disease, reticulosis or nonlipid histiocytosis).

2. It may appear in children or adults in a chronic form in which the histiocytic lesions, again not usually limited to the skeleton, tend to undergo collagenization and lipidization and in which the prognosis is often grave because of the likelihood of damage to the brain or pituitary gland (Schüller-Christian disease or lipogranulomatosis).

From the Division of Dermatology, University of Minnesota, H. E. Michelson M. D., Director.

1. Wallgren, A.: Systemic Reticulo-Endothelial Granuloma, Am. J. Dis. Child. **60**:471-500 (Sept.) 1940.

2. Farber, S.: The Nature of "Solitary or Eosinophilic Granuloma" of Bone, Am. J. Path. **17**:625-629, 1941.

3. Mallory, T. B.: Medical Progress: Pathology; Diseases of Bones, New England J. Med. **227**:955-960, 1942.

4. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone, Arch. Path. **37**:99-118 (Feb.) 1944.

3. It may appear in children or young adults in a comparatively benign and much more localized form in which the lesions occur chiefly in the skeleton (often only in a single bone) and heal readily after simple curettage, even without any therapeutic intervention (eosinophilic granuloma of bone).

### LETTERER-SIWE DISEASE (ACUTE OR ALEUKEMIC RETICULOSIS, NONLIPID HISTIOCYTOSIS)

Letterer,[5] in 1924, under the title "Aleukämische Retikulose (Ein Beitrag zu den poliferativen Erkrankungen des Retikuloendothelialapparates)," discussed a disease characterized by splenohepatomegaly, associated with anemia and a purpuric eruption in an infant 6 months of age. Within four days after admission to the hospital the child died, and (postmortem) histologic examination showed proliferation of large pale reticuloendothelial cells invading and replacing the normal structure of the spleen, lymph nodes, liver, bone marrow and skin. From 1924 to 1933 several similar cases were reported. In the latter year Siwe[6] reported an additional case in a 16 month old infant and grouped them all into a well defined clinicopathologic entity. Abt and Denenholz,[7] in an exhaustive report in 1936, coined the term Letterer-Siwe disease.

Siwe[6] listed the following features as characteristic of this disease:

1. There is a distinct enlargement of the spleen and moderate to considerable hepatomegaly.

2. A hemorrhagic tendency as manifested by purpura is a constant observation.

3. Localized tumors of bones may be present, recognizable in certain cases only roentgenologically or at autopsy.

4. There is secondary anemia of a progressive nonregenerative type, a normal or diminished leukocyte count and a normal differential and platelet count.

5. There is generalized, painless and discrete lymphadenopathy.

6. Splenic puncture may show an increased number of non-lipid-containing macrophages.

7. The disease, which is neither hereditary nor familial, occurs exclusively in infants. The onset is acute, and the course is downhill,

---

5. Letterer, E.: Aleukämische Retikulose, Frankfurt. Ztschr. f. Path. **30**:377-394, 1924.

6. Siwe, S.A.: Die Reticuloendotheliose=ein neues Krankheitsbild unter den Hepatosplenomegalien, Ztschr. f. Kinderh. **55**:212-247, 1933.

7. Abt, A. F., and Deneholz, E. J.: Letterer-Siwe's Disease: Splenohepatomegaly Associated with Widespread Hyperplasia of the Nonlipoid-Storing Macrophages; Discussion of So-Called Reticulo-Endothelioses, Am. J. Dis. Child. **51**:499-522 (March) 1936.

the condition lasting from a few weeks to several years. The cause is unknown.

8. The histologic observations consist of generalized hyperplasia of pale round non-lipid-storing mononuclear macrophages, containing eccentric chromatic nuclei. The spleen, liver, lymph nodes, bones, lungs and skin are the organs most commonly affected.

### SCHUELLER-CHRISTIAN DISEASE (LIPOGRANULOMATOSIS)

Schüller-Christian disease was first described by Schüller[8] in 1915 and elaborated on by Christian[9] in 1919 and Rowland[10] in 1928. In 1893 Hand[11] described a case in which there were osseous defects in the skull, exophthalmos and polyuria, which he attributed to tuberculosis, although more likely it was the same process later described by Schüller and Christian. Since the early descriptions, it has been frequently contended that diabetes insipidus, exophthalmos and lacunar lesions in the calvarial bones represented the triad of characteristic cardinal symptoms. Following the works of Rowland[10] and Epstein[12] it was apparent, especially from histologic studies, that the disease might appear in various other forms. In some cases, all three of the cardinal symptoms were absent and involvement occurred in entirely different organs. Because of the great diversity in the manifestations, Henschen[13] classified Schüller-Christian disease into eight types: (1) the typical triad (diabetes insipidus, exophthalmos and cranial lesions), (2) the same without diabetes insipidus, (3) the same as (1) without exophthalmos, (4) skeletal changes without diabetes insipidus or exophthalmos, (5) diabetes insipidus and exophthalmos without skeletal changes, (6) xanthomatosis with disturbances of growth, (7) xanthomatosis without any of the other aforementioned symptoms and (8) xanthomatosis exclusively of the skin. The histologic observation of large numbers of cholesterol-containing foam cells is the feature common to all the various types. Not only is there great diversity in the clinical manifestations of

8. Schüller, A.: Ueber eigenartige Schadeldefekte im Jugendalter, Fortschr. a.d. Geb. d. Röntgenstrahlen **23**:12-18, 1915.

9. Christian, H. A.: Defects in Membranous Bones, Exophthalmos, and Diabetes Insipidus, in Contribution to Medical and Biological Research, New York, Paul B. Hoeber, 1919, vol. 1, pp. 391-401.

10. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System, Arch. Int. Med. **42**:611-674 (Nov.) 1928.

11. Hand, A.: Polyuria and Tuberculosis, Arch. Pediat. **10**:673 (Aug.) 1893.

12. Epstein, E.: Die generalisierten Affektionen des histozytären Zellensystems (Histiozytomatosen), Med. Klin. **21**:1501-1542, 1925.

13. Henschen, F.: Ueber Christians Syndrom und dessen Beziehungen zur allgemeinen Xanthomatose, Acta peadiat. (supp. 6) **12**:1-93, 1931.

Schüller-Christian disease but its course varies from a relatively benign one which eventuates in healing to a malignant course which leads to death.

### EOSINOPHILIC GRANULOMA OF BONE

In 1940 Lichtenstein and Jaffe[14] described a disease characterized by a solitary bone lesion, which they regarded as inflammatory in nature, and assigned to it the title of "eosinophilic granuloma of bone," because of its histologic characteristics. About the same time Otani and Ehrlich[15] described the same disease, independently of Lichtenstein and Jaffe[14], under the name "solitary granuloma of bone." Otani and Ehrlich[15] expressed the opinion that trauma was an important causative factor. In a later report Jaffe and Lichtenstein[4] stated that shortly after the publication of their first paper they encountered cases with multiple lesions of the same type as previously described. Farber[2] (1941) and Green and Farber[16] (1942) confirmed the occurrence of both single and multiple skeletal lesions. The clinical features were discussed in detail, and the peculiar granulomatous character of the pathologic infiltrate was emphasized.

Eosinophilic granuloma occurs in children and young adults. Roentgenologically, single lesions simulate bone cyst, osteomyelitis or malignant growth. Multiple lesions suggest multiple myeloma or malignant growth, but in roentgenograms they are indistinguishable from the lesions of Schüller-Christian disease (Green and Farber[16]). With the possible exception of the bones of the hands and feet, almost any bone may be affected with the appearance of either single or multiple lesions. In the latter the cranial vault, ribs, vertebrae or the long bones, such as the humerus or femur, may be involved. Constitutional symptoms are absent, although local complaints, such as tenderness and pain arising from the skeletal lesions, are often present. The symptoms may be of only a few days', several weeks' or several months' duration when the patient is first seen. Leukocytosis of moderate severity is occasionally seen, without change in the differential count.

Green and Farber[16] stated that the histologic observations varied from "eosinophilic granuloma" in lesions of short duration to "lipogranuloma" in older lesions; they interpreted them as being identical with the lesions in certain stages of Schüller-Christian disease. His-

14. Lichtenstein, M. D., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, Am. J. Path. **16**:595-604, 1940.

15. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone Simulating Primary Neoplasm, Am. J. Path. **16**:479-490, 1940.

16. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, J. Bone & Joint Surg. **24**:499-526. 1942.

tiocytes constitute the basic component of the lesions, although eosinophils give it a striking imprint, especially when present in large numbers. Later the histiocytes assume the character of lipophages and take on the typical appearance of foam cells.

Ordinarily the lesions of eosinophilic granuloma heal promptly after roentgen irradiation and occasionally after curettage.

### CUTANEOUS LESIONS IN SYSTEMIC RETICULOENDOTHELIAL GRAULOMA

In Letterer's case (1924), in a 6 month old infant, there was high grade purpura with "hemorrhagic diathesis" at postmortem examination. Histologic examination showed hemorrhage plus necrosis of the epidermis and proliferation of large cells. Although there was some hemorrhage in the epidermis, it was located chiefly in the papillary portion of the cutis. The areas of hemorrhage occurred as intermittent streaks in certain areas or as continuous masses extending to the middle layer of the cutis in other places. The proliferation of large cells was fairly widespread, either in relatively small foci or in broad sheets in the papillary portion of the cutis and penetrating the papillae. The epidermis overlying these foci was necrotic. The proliferation of the large cells was seen simultaneously with the bleeding, the latter apparently depending somewhat on the penetration and growth of the cells in the adventitial layer of the vessels. This cellular proliferation was observed not only as mantles about the vessels but also around the hair follicles and even about the more deeply lying sweat glands. Other authors have noted purpura in Letterer-Siwe disease, including Guizetti,[17] whose patient showed numerous punctiform hemorrhages on the trunk and lower extremities. Podvinec and Terplan[18] also noted extensive cutaneous hemorrhage in a similar case. In classifying and grouping these cases, which had been described under various titles, such as aleukemic reticulosis, acute or infectious aleukemic reticulosis and reticuloendotheliosis, Siwe[6] (1933) and later (1936) Abt and Denenholz[7] stressed the consistent tendency to hemorrhage, manifested chiefly by petechiae or purpura. Uher,[19] Roussy and Oberling[20] and Foot and Olcott[21] reported similar ob-

17. Guizetti, H. U.: Zur Frage der infektiös bedingten Systemerkrankungen des reticuloendothelialen Apparates in Kindesalter, Virchows Arch. f. path. Anat. **282**:194-208, 1931.

18. Podvinec, E., and Terplan, K.: Zur Frage der sogenannten akuten aleukämischen Retikulose, Arch. f. Kinderth. **93**:40-55, 1931.

19. Uher, Z.: Ein Beitrag zu den sogenannten Reticuloendotheliosen, Virchows Arch. f. path. Anat. **289**:504-509, 1933.

20. Roussy, G., and Oberling, C.: Akute, wahrscheinlich infektiöse aleukämische Retikulose bei einem Säugling, Wien. med. Wchnschr. **84**:407-413, 1934.

21. Foot, N. C., and Olcott, C. T.: Report of a Case of Non-Lipoid Histiocytosis (Reticuloendotheliosis) with Autopsy, Am. J. Path. **10**:81-96, 1934.

servations. Not in every case of Letterer-Siwe disease are there purpuric lesions, however, as exemplified by the cases of Schultz, Wermbter and Puhl,[22] Uehlinger[23] and Klostermeyer.[24] The patient of Podvinec and Terplan[18] also presented necrotic ulcerating angina along with extremely pale skin studded with petechiae.

Patients with Schüller-Christian disease, according to Chester and Kugel (1932),[25] may present one or a combination of five types of cutaneous lesions: bronze pigmentation, papulopustular eruption, purpura, seborrhea-like lesions and lipid infiltration of the eyelids. Cutaneous lesions occur in about one third of the cases. Lane and Smith[26] (1939) succinctly discussed the various cutaneous manifestations of this disease. They reported clinical and postmortem observations in 4 cases which belonged in the group of systemic reticuloendothelial granuloma. Three of their older patients (up to 3 years and 5 months) had the Schüller-Christian type, while the youngest of the group apparently had the acute fatal form of the disease (Letterer-Siwe type). The latter patient had the disease at birth and died at the age of 6 weeks. The liver and spleen were enlarged; there was diffuse hemorrhagic exanthem, and a roentgenogram of the chest showed parenchymatous infiltration of the lungs. There was no exophthalmos, no defects in the membranous bones and no polyuria. Two of the other 3 patients presented cutaneous lesions. In 1, a 3 year old girl, there was a striking papular eruption distributed profusely over the trunk and present also on the scalp, forehead, axillas, arms and palms. The papules were red, but some were tinged with yellow or brown. They were circular, slightly infiltrated and from 1 to 4 mm. in diameter. There were scaly lesions on the scalp and petechiae on the palms and soles. The eruption somewhat simulated lichen scrofulosorum. The other patient, a girl aged 14 months, presented a nonhealing ulcer of the hard palate and an ulcer in the groin, plus a papular eruption on the face, the neck, the trunk and, to a less extent, the extremities. The lesions on the trunk coa-

22. Schultz, A.; Wermbter, F., and Puhl, H.: Eigentümliche granulomartige Systemerkrankung des hämatopoetischen Apparates (Hyperplaise des retikuloendothelialen Apparates), Virchows Arch. f. path. Anat. **252**:519-549, 1924.

23. Uehlinger, E., Aleukämische Reticulose, Beitr. z. path. Anat. u.z. allg. Path. **83**:719-746, 1930

24. Klostermeyer, W.: Ueber eine sogenannte aleukämische Reticulose mit besonderer Beteiligung des Magen-Darmkanales, Beitr, z. path. Anat. u. z. allg. Path. **93**:1-10, 1934.

25. Chester, W., and Kugel, V. H.: Lipoidgranulomatosis (Type, Hand-Schüller-Christian): Report of a Case, Arch. Path. **14**:595-612 (Nov.) 1932.

26. Lane, C. W., and Smith, M.: Cutaneous Manifestations of Chronic (Idiopathic) Lipoidosis (Hand-Schüller-Christian Disease), Arch. Dermat. & Syph. **39**:617-644 (April) 1939.

lesced to form plaques. The individual lesions were bright red and measured 1 to 3 mm. in diameter.

The histologic observations in all cases were similar and consisted of an accumulation of large mononuclear cells with irregularly shaped vesicular nuclei and eosin-staining cytoplasm in lesions of short duration. There were a few lymphocytes intermixed with the larger cells. These groups of large cells were situated in the upper portions of the cutis beneath the epidermis. In places they seemed to be about vessels, while in other areas they were in sheets or bands. In older lesions the cells assumed a distinctly foamy appearance. Islands of normal tissue were interspersed among the groups of abnormal cells. When the foci became larger, hemorrhage occurred in and about the cellular masses. In some places the masses seemed to encroach on the epidermis to the extent of producing necrosis. Lane and Smith[26] stated the belief that the two types of eruption which most commonly occurred in Schüller-Christian disease were the petechial and diffuse papular types. In addition to hemorrhagic and papular types of exanthem, Chester and Kugel,[25] Rowland,[10] Ceelen,[27] Gerstel,[28] Wätjen[29] and Lichty[30] observed xanthomatous nodules and papules, eruptions simulating seborrheic eczema, especially on the scalp, and mucosal ulcerations.

Cutaneous hemorrhage dominates the picture in the acute fulminating Letterer-Siwe type, whereas, diffuse papular and seborrhea-like eruptions are commoner in the Schüller-Christian type. It is noteworthy that the cutaneous lesions in both of our cases closely simulated keratosis follicularis.

At the annual meeting of the Central States Dermatologic Section in Detroit, April 1946, a case of eosinophilic granuloma of bone with cutaneous lesions was presented by Wile and Curtis.[31] The patient was a girl, aged 3, in whom an eruption appeared on the scalp at the age of 8 months. Shortly thereafter a papular eruption developed on the buttocks and genitals, and painful eroded lesions appeared in the mouth. When the child was first seen, in September 1944, there were sharply demarcated depigmented areas on the hard palate and pos-

27. Ceelen, W.: Ueber die Lipoidgranulomatose (Hand-Schüller-Christiansche Krankheit), Deutsche med. Wchnschr. **58**:680-681, 1933.

28. Gerstel, G.: Ueber die Hand-Schüller-Christiansche Krankheit auf Grund gänzlicher Durchuntersuchung des Krochengerüstes, Virchows. Arch. f. path. Anat. **294**:278-303, 1934.

29. Wätjen, A. J.: Beitrag zur Kenntnis des Morbus Schüller-Christian, Beitr. z. path. Anat. u.z. allg. Path. **96**:443-465, 1936.

30. Lichty, D. E.: Lipoids and Lipoid Diseases: Zanthomatosis (Schüller-Christian's Type), Arch Int. Med. **53**:379-390 (March) 1934.

31. Wile, U., and Curtis, A.: Case Presentation at Annual Meeting of Central States Dermatological Society, Detroit, April 27, 1946.

terior portion of the tongue. Moist granulomatous masses, 2 to 3 cm. in diameter, were present in each axilla. Red scaly papules were seen in the groins, and the anogenital region was denuded and oozing.

Roentgenologic examination disclosed destructive lesions in the right second rib and left ilium. A similar lesion developed later in the right mastoid.

Histologic examination of several lesions showed an infiltration of large mononuclear cells and many eosinophils in the cutis.

The cutaneous and osseous lesions healed following roetngen ray therapy.

Epstein[32] has also observed a similar case.

## REPORT OF CASES

CASE 1.—J. S., a white boy aged 9 months, was admitted to the University Hospitals Sept. 8, 1945, because of diarrhea, which began three weeks prior to admission, and an eruption of the scalp, face, neck and trunk, present since the infant was 2 months old.

The child was a full term normal baby. At the age of 2 weeks, a greasy scaling eruption appeared on the scalp, which remained the same for two months when a similar process appeared on the trunk. At the age of 4 months the skin became almost entirely clear and remained so until three weeks prior to hospital admission. At that time abdominal pain, accompanied with diarrhea, developed and continued until admission to the hospital. There was progressive loss of weight.

*Physical Examination.*—On admission there was evidence of loss of weight, the turgor of the skin was poor, the eyes and fontanels were sunken and respirations were rapid. Examination of the head showed moderate asymmetry, and there appeared to be a bony defect in the region of the right parieto-occipital junction. There was no exophthalmos. There was a crusted eruption resembling seborrheic dermatitis on the forehead and scalp and extending downward behind both ears. There were a few petechiae in both popliteal spaces and in the left cubital fossa. Examination of the extremities showed moderate soft tissue swelling at the upper end of the left tibia. No other abnormalities were noted.

On October 5, the total cholesterol level was 112 mg., of which cholesterol esters were 57 per cent. All other laboratory data were normal.

Roentgenologic examination showed a cystic-appearing destructive lesion in the proximal end of the left tibia, beginning at the proximal end of the diaphysis and extending downward for about 7 cm. The shaft was expanded, and in some areas the cortex was completely destroyed. There was periosteal new bone formation along the lower margin of the lesion. The other long bones of the lower extremities appeared normal. A single roentgenogram of the right arm showed a cystic appearance at the distal end of the humerus. Roentgenograms of the chest on September 13 showed some increased mottling of both lungs, the exact nature of which was not apparent, but which was interpreted as fibrosis. Examination of the pelvic bones on September 17 showed a small area of rarefaction in the upper portion of the shaft of the left femur, similar to the areas seen elsewhere in the long bones. There was no evidence of disease in the pelvis itself. A roentgenogram of the skull on September 17 showed two definite areas of destruction.

32. Epstein, S.: Personal communication to the authors.

*Course in Hospital.*—The lesions of the bones were treated with filtered roentgen rays. By October 17, the cutaneous eruption had almost entirely disappeared, but there was considerable scarring in the involved areas. The child had regained his admission weight and was discharged, to be followed up in the outpatient department.

Within a few days after discharge, there was an exacerbation of the cutaneous lesions in the previously involved areas. Between Oct. 31, 1946, and December 26, three superficial treatments with roentgen rays were administered to the sides of the face, abdomen and groins, but little improvement was noted.

Fig. 1 (case 1).—Seborrhea-like eruption on the face. The patient also had papular lesions on the trunk simulating keratosis follicularis.

On December 26, the child was readmitted to the hospital because of an infection in the upper part of the respiratory tract and an exacerbation of the dermatitis. At this time the cholesterol level was 152 mg. and cholesterol esters 103 mg. per hundred cubic centimeters. By January 8, the coryza had completely disappeared, the cutaneous lesions had improved and the child was discharged.

He was seen in the outpatient clinic from January 8 until March 22. Until March 9, he maintained a fairly stable course. On March 26, he was readmitted

because of progressive loss of weight, increasing anemia and the appearance of numerous petechiae and ecchymoses on the arms and legs. The scalp and trunk were covered by a diffuse, greasy, scaly, erythematous eruption. Both eyes were sunken, but there was a relative exophthalmos of the right eye. The patient died on the third hospital day.

*Essential Observations at Autopsy.*—The child had a generalized eruption. The scalp was covered by greasy scales. The eczematous process was sharply localized to the groins and axillas. The arms and forearms, as well as the thighs and buttocks, showed many petechial hemorrhages. The palms were excoriated. On palpation of the skeletal system for bony defects, one defect, measuring 2 by 3 cm., was noted in the right temporal region lateral to the orbit, as well as one in the right occipital region, measuring 3 by 5 cm. There was a soft mass overlying this area. The anterior surface of the left tibia showed a longitudinal scar, measuring approximately 4 cm. in length. There were soft fluctuant areas underlying this region.

The spleen weighed 115 Gm. and had a diffusely purple appearance. On cut section, each surface showed multiple small fatty nodules, varying from 1 mm. to 1 cm. in diameter.

A creamy yellow exudate was liberated on incision of the left anterior aspect of the left tibia. Numerous silk sutures were recovered from the bed of the old operative site. The left tibia itself appeared to be structurally intact.

Examination of the skull showed two large firm red lymph nodes subcutaneously overlying the region of the bony defect in the right occipital region. The arachnoid membrane overlying the right and left parietal lobes of the brain was thickened and had a yellow fatty appearance.

Microscopic Examination: The following tissues were normal: kidney, stomach, liver, heart, bladder, pancreas and adrenal glands. Microscopic sections of the left tibia taken from the region of the previous biopsy showed no evidence of any tumor. A portion of tissue adjacent to the dura in the region of the occipital bony defect showed diffuse degeneration of connective tissue, lipid droplets, much nonspecific pigment with newly formed connective tissue and occasional giant cells. The spleen showed moderate growth of reticuloendothelium in the splenic corpuscles. There was much pigment present, with a moderate number of lipid-containing cells. The lung showed gross emphysema and atelectasis, with masses of reticuloendothelial cells filling the septal walls. There was diffuse thickening in the interstitial tissues, and foam cells were present.

Histologic Examination: A brownish red papule from the thorax was removed with a cutaneous punch, fixed in solution of formaldehyde, embedded in paraffin and sectioned in the usual manner. At the time the biopsy was performed the patient was not on the dermatology service, and, unfortunately, stains for fat were not done.

In sections stained with hematoxylin and eosin it could be seen immediately that the most outstanding changes were in the papillary portion of the cutis directly beneath the epidermis. Here were masses of large monocytic cells with eosin-staining cytoplasm and irregularly shaped nuclei. The cells were not densely packed in most places, and the clear spaces between them gave a syncytial or foamy appearance to the entire affected zone. There were a few lymphocytes interspersed among the monocytes. In the sections which we examined, the monocytic cells were not arranged especially about blood vessels but in a bandlike focus which extended up to the basal layer and in many places disrupted it entirely.

The epidermis overlying the infiltrate was thinner than in other areas and showed much vacuolization. In many places there was no sharp line of demarcation between the monocytic infiltration and the epidermis, the one seeming to fuse into the other. In the particular sections which we examined the process had not extended so far as to produce hemorrhage and necrosis of the epidermis.

In the portions of the cutis below the zone of monocytic cells there was only dilatation of vessels with perivascular lymphocytic mantles.

CASE 2.—M. M., a 2½ year old white boy, was first admitted to the University Hospital on May 14, 1943,, for investigation and treatment of generalized dermatosis, present since the patient was 9 months of age. At that time a generalized eruption appeared, characterized by small discrete papules. The nature of the eruption changed within a short time, so that the scalp lesions resembled seborrheic dermatitis and the lesions on the rest of the body, especially on the trunk, became

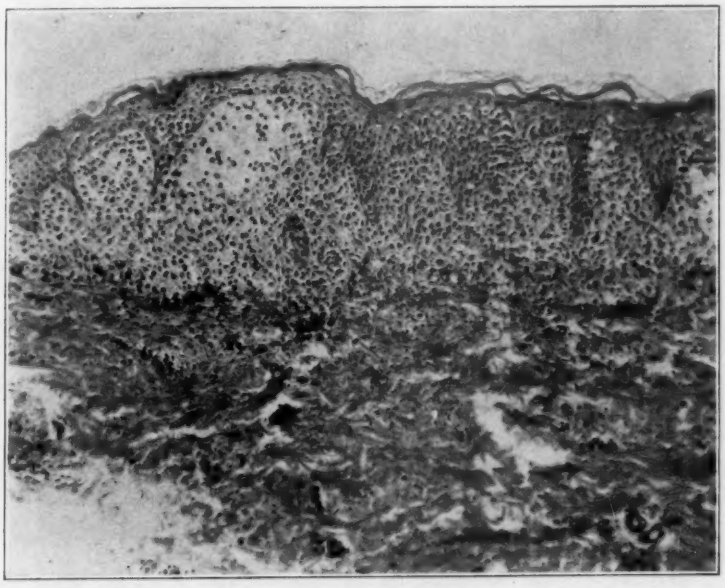


Fig. 2 (case 1).—Section showing a band of large clear mononuclear cells in the papillary portion of the cutis.

eczematous. Two and a half weeks before admission purulent material began to drain from the left thumb. Within a few days similar drainage was noted from all of the fingers. There was also an infection of the gums and enlargement of both axillary and inguinal lymph nodes.

*Physical Examination.*—On admission the temperature, pulse rate and respirations were normal. The skin was pale and dry, with several small achromic spots on the neck and chest and in both axillas and groins. The scalp showed much crusting as well as a few pustules in both posterior auricular areas. Both occipital and anterior cervical nodes were enlarged, discrete and tender. There was moderate exophthalmos of the left eye. There was a purulent fetid discharge from both ears. The liver was palpable for 2 cm. below the costal margin, and the edge was smooth and tender. The spleen was palpable about 1cm. below the costal margin. There was a small anal ulcer, about 2 cm. in diameter, extending upward into the

rectal mucosa. The subungual areas of the fingers showed extensive abscess formation. A biopsy of a cervical node showed hyperplasia of the reticulum, destroying much of the architecture of the node. The subcapsular sinus was obliterated. Occasional large reticular giant cells were seen. The lymph node imprints and the imprints and the appearance of the section were compatible with a diagnosis of Schüller-Christian disease.

The child was discharged from the hospital June 4, following which he received a series of treatments with filtered roentgen rays, to the lateral left mastoid and left orbit. On October 25, roentgenograms of the right knee showed some rarefaction in the medulla of the femur just above the epiphysis, suggestive of Schüller-Christian disease. On November 10, there was considerable swelling of the right knee. The left inguinal nodes were swollen and tense, but not suppurating. The right inguinal nodes continued to drain. Further roentenologic examination on

Fig. 3 (case 2).—A male infant aged 15 months with a crusted seborrhea-like eruption on the scalp and a purpuric papular eruption on the trunk simulating keratosis follicularis.

this date showed multiple destructive areas in the right mastoid, more distinct than on previous examination, but no larger. The long bones, except at the right knee, were studied and were observed to be normal roentgenologically. The infant was readmitted November 29 for sternal biopsy, which showed an increase of the myeloid elements, and single, multinucleated and plasma cells were numerous. There were a few lipid-filled reticuloendothelial cells.

The child was readmitted to the hospital on December 22, because of abscesses in both groins, with beginning gangrene of the tissues around the groin. His condition became critical on the evening of admission, and he died early the following day.

*Essential Observations at Autopsy.*—There were crusted lesions on the scalp and trunk. A necrotic defect, measuring 3 by 7 cm., was present in the right inguinal region. Another, measuring 4 cm. in diameter, was present in the left inguinal

region near the superior aspect of the spine. Grayish black necrotic tissue protruded to about 1 cm. above the level of the skin from these defects.

The calvarium appeared normal. The anterosuperior portion of the right petrous bone was replaced by tumor tissue. The defect of the mesial portion of the right supraorbital plate was also replaced by similar tissue. The intraocular contents appeared normal. Atrophy and destruction of the alveolar processes, with loosening of the teeth, were also present.

Microscopic Examination: The retina and choroid appeared normal, and the optic nerve showed no invasion, but foam cells were present in the surrounding connective tissues.

The interalveolar tissue of the lung was enormously increased and consisted of fibrous connective tissue and lipid-filled reticuloendothelial cells.

In the spleen, overgrowth of reticulum was most apparent about the arterioles and in some instances replaced the malpighian corpuscles entirely. There were many foam cells.

In the liver fatty metamorphosis was far advanced, involved the portal and periportal spaces and continued from one to the other with normal-appearing hepatic parenchyma about the central vein.

Macrophages, some of which contained lipid, were numerous in a mesenteric lymph node. Foam cells were present in the periadrenal fat. Section of sternal marrow showed that most of it was replaced by fibrous connective tissue and lipid-containing foam cells. Section of the lower end of femur showed a few lipid-laden reticuloendothelial cells.

## COMMENT

In a consideration of the systemic reticuloendothelial granulomas, several questions arise: (1) Are Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma of bone entirely separate diseases or do they represent only different manifestations of the same basic disorder of the reticuloendothelial system? (2) Should Schüller-Christian disease be removed from the lipoidoses? (3) Should eosinophilic granuloma of skin be grouped with eosinophilic granuloma of bone and in turn with the systemic reticuloendothelial granulomas?

When the course and symptoms of Letterer-Siwe disease and Schüller-Christian disease are analyzed and compared, one is struck with the lack of concrete evidence that they are entirely separate diseases. There has been no exception to the rule that Letterer-Siwe disease is invariably fatal, and it usually, but not invariably, runs a rapid course. Schüller-Christian disease frequently is more chronic, and an estimated 30 per cent of patients recover. The disease can be rather rapidly fatal, however. Thus, the course of Schüller-Christian disease may vary greatly from relative benignity to extreme malignancy. Progressive anemia, a distinct hemorrhagic tendency, hepatosplenomegaly, lymphodenopathy, lesions of the bones and fever are the symptoms which characterize Letterer-Siwe disease, yet every one of these symptoms has been encountered in cases in which the diagnosis was Schüller-Christian disease. Lichty's[30] case exemplified this point. Cases of Schüller-Christian

disease with these symptoms occur in infants or young children, and the disease runs a relatively rapid fatal course.

For many years it was contended that the triad of symptoms of diabetes insipidus, exophthalmos and osseous lesions of the skull characterized Schüller-Christian disease. The works of Rowland[10] and Epstein,[12] as mentioned previously, stressed the fact that the symptomatic pictures were widely diversified and that one or all of the cardinal symptoms might be completely lacking. In many cases the changes occur in entirely different organs, and, since the symptoms depend to a certain extent on the localization of the lesions, the picture is subject to wide variation. In Letterer-Siwe disease the complete triad of symptoms regarded as characteristic of Schüller-Christian disease (exophthalmos, diabetes insipidus and cranial lesions) is apparently extremely rare, although Jaffe and Lichtenstein[4] stated that it has occurred. It has been mentioned as a differential point that the osseous lesions in the two diseases are different, the skull being affected in Schüller-Christian disease and the long bones or ribs in Letterer-Siwe disease. This patient presented osseous lesions of the cranium. Jaffe and Lichtenstein[4] also mentioned lesions of the skull in Letterer-Siwe disease. In the case reported by Schultz, Wermbter and Puhl,[22] there were not only osseous defects in the skull but exophthalmos. In contrast, numerous cases of Schüller-Christian disease have been recorded in which there were lesions in the long bones but not in the skull. The cutaneous lesions in Letterer-Siwe disease and Schüller-Christian disease offer no good means of differentiation, since in both the eruption tends to be hemorrhagic.

It has been emphasized previously that Schüller-Christian disease is extremely varied in its course, localizations and clinical manifestations. The most constant feature is the histologic picture characterized by granulomatous tissue containing large numbers of lipid-containing foam cells. This had led to a fairly widely accepted concept that the disease belongs to the systemic lipoidoses and is closely linked to Gaucher's disease and Niemann-Pick disease. The three diseases have been differentiated not only by their clinical course and symptoms but by the type of lipid contained in the cells—cholesterol in Schüller-Christian disease, diaminophosphatides (sphingomyelin) in Niemann-Pick disease and cerebrosides (especially kerasin) in Gaucher's disease.

Wallgren[1] pointed out that close study of the reports of necropsy and case histories led to doubt as to whether the storage of lipid in the reticulum cells in Schüller-Christian disease could be regarded as an essential or usable point in differentiating Schüller-Christian disease from the other reticuloendothelial granulomas. Wallgren[1] emphasized that in Schüller-Christian disease the masses of proliferated reticulum cells may show large numbers of cholesterol-containing

foam cells in certain organs while in others they may be entirely absent. It would thus seem that, if a proliferation of reticulum cells can take place without a trace of local accumulation of lipid, the view that Schüller-Christian disease is a primary disturbance of cholesterol metabolism can hardly be correct. Furthermore, hypercholesterolemia is inconstant in Schüller-Christian disease and can be explained as a phenomenon secondary to the proliferation of reticulum cells.

If one accepts the thesis that the histologic picture is the one constant diagnostic feature of the disease, every patient should show, as the anatomic prerequisite, lipidized lesions classifiable as lipogranuloma. Such is not the case, however, since examinations in early stages of the disease proved later (at autopsy) to be Schüller-Christian disease have shown only nonlipid reticuloendotheliosis. Jaffe and Lichtenstein[4] have emphasized the fact that lipidization of the lesions in Schüller-Christian disease occurs relatively late in the course of the disease. These observations by various workers argue against classifying Schüller-Christian as a primary type of lipoidosis as well as against the view that accumulation of lipid in the lesions is an essential feature, since it is definitely inconstant. Such observations also lead one to believe that the disease is a basic disturbance of the reticuloendothelial system and that lipidization is secondary. The cause of both Letterer-Siwe disease and Schüller-Christian disease remains obscure.

Since lipidization of the lesions seems to occur not at the beginning but later in the course of these reticuloendothelial granulomas, the view of Flori and Parenti,[33] Glanzmann,[34] Mallory,[3] Wallgren[1] and Jaffe and Lichtenstein[4] that lipidization is slight or absent in Letterer-Siwe disease because it runs a malignant course and ends fatally in a short time seems well grounded. Jaffe and Lichtenstein[4] stated that in some cases in which the disease was diagnosed as Letterer-Siwe disease, which had lasted over a year, transformation of histiocytes into lipophagic foam cells has been noted. Farber,[3] Green and Farber[16] and Jaffe and Lichenstein[4] have suggested that eosinophilic granuloma of bone should be linked with the conditions just discussed. Jaffe and Lichtenstein[4] reported a case in a 9 month old girl which was diagnosed clinically as Letterer-Siwe disease, in which the histologic picture of destructive lesions in the radius was

33. Flori, A. G., and Parenti, C. G.: Reticuloendoteliosi iperplasica infettiva ad evoluzione granulo xantomatosa (tipo Hand-Schüller-Christian), Rov. di clin. pediat. **35**:193-263, 1937.

34. Glanzmann, E.: Infektiose Retikuloendotheliose (Abt-Letterer-Siwe'sche Krankheit) und ihre Beziehungen zum Morbus Schüller-Christian, Ann. pediat. **155**:1-8, 1940.

completely indistinguishable from such tissue in corresponding lesions of eosinophilic granuloma of bone. The diagnosis in this case was confirmed at autopsy. Hemorrhage, necrosis and large fields of histiocytes interspersed with eosinophils constituted the histologic picture of bone lesions. Why the lesions in the lymph nodes and internal organs fail to show these observations has as yet not been explained.

Those who have studied eosinophilic granuloma of bone agree that the roentgenologic observations cannot be differentiated from Letterer-Siwe disease or Schüller-Christian disease, especially when there are lesions of the skull.

Eosinophilic granuloma of the skin has been discussed in recent communications by Buley,[35] Lewis and Cormia,[36] and Weidman.[37] According to Buley,[35] Martinotti[38] first described this condition in 1923, when he published a study on the histogenesis of eosinophils. Lewis and Cormia[36] credited Freund with having described the first case in 1930. The disease is exceedingly rare, and, according to Buley[35] who reported a case in 1946, there were only 9 previously recorded cases in the literature. The actual number of cases of true eosinophilic granuloma of skin is probably even less, since Lewis and Cormia[36] expressed the belief that some of the cases reported under that title were improperly labeled.

Cutaneous eosinophilic granuloma is characterized by doughy to firm red, bluish red or brownish red nodules, plaques or tumefactions, which may be smooth, verrucous or ulcerated. Lesions have been reported on the face, trunk and extremities. The peripheral blood carries a higher number of eosinophils (8 to 55 per cent).

The chief histologic observations are in the cutis and consist of a dense infiltrate which is predominantly eosinophilic, with some lymphocytes, monocytes, histiocytes and plasma, mast, giant and epithelioid cells. The infiltrate occurs not only about the blood vessels but around sweat ducts, hair follicles and sebaceous glands. In well developed lesions the blood vessels show extensive endarteritis and thickening, with either diminution in the size of, or complete obliteration of, the lumens.

As a rule the patient's general condition remains unaffected. The disease is apparently not malignant. In some cases cures have been

35. Buley, H. M.: Eosinophil Granuloma of the Skin, J. Invest. Dermat. **7**:291-300, 1946.

36. Lewis, G. M., and Cormia, F. E.: Eosinophilic Granuloma: Theoretic and Practical considerations Based on the Study of a Case, Arch. Dermat. & Syph. **55**: 176-193 (Feb.) 1947.

37. Weidman, F. D.: The "Eosinophilic Granulomas" of the Skin, Arch. Dermat. & Syph. **55**:155-175 (Feb.) 1947.

38. Martinotti, L.: Contributo allo studio della eosinofilia istiogenica cutanea, Arch. per le Sc. Med. **46**:295, 1923.

reported following treatment with roentgen rays, excision or the administration of arsenic, although the disease in the cases of Buley[35] and Lewis and Cormia[36] was slowly progressive or resistant to treatment.

Practically nothing is known regarding the cause and pathogenesis of eosinophilic granuloma. Buley[35] expressed the opinion that, for the sake of clarity, eosinophilic granuloma should be grouped separately among the other types of reticuloendotheliosis as long as there is not more known concerning the origin and function of eosinophils. Lewis and Cormia's[36] patient had a Trichophyton purpureum infection of the feet. During vigorous treatment of the dermatophytosis there was definite exacerbation of the eosinophilic granuloma on three occasions. Similar exacerbation followed an injection of trichophytin, and typical eosinophilic granuloma developed at several sites of injection. Lewis and Cormia[36] also pointed out the striking similarity in the histologic observations in eosinophilic granuloma and periarteritis nodosa. They felt that the initial and fundamental pathologic change was in the blood vessels and suggested the term eosinophilic periareritis instead of eosinophilic granuloma. This fundamental change would not militate against alining cutaneous eosinophilic granuloma with the osseous form, since in the latter the process apparently starts as a proliferation of reticulum cells in the adventitia of the blood vessels in the marrow. The cases of Wile and Curtis[31] and Epstein[32] suggest that the cutaneous and osseous manifestations are all part of a basic disorder of the reticuloendothelial system. Lewis and Cormia[36] stated that eosinophilic granulomatous tumors in the bones, lungs and reticuloendothelial system were "somewhat comparable" to the lesions of the skin. This includes, especially, eosinophilic granuloma of bone and so-called Loeffler's syndrome in the lung (transient recurrent pulmonary infiltrations accompanied with eosinophilia, cough, mild fever and asthma). These authors would rather not group cutaneous eosinophilic granuloma with Letterer-Siwe disease, however, because of the transition of the latter to Schüller-Christian disease, which they regarded as probably unrelated. This phase of the problem has been discussed previously. Because of our present lack of knowledge about these conditions, it is impossible to draw final conclusions concerning their interrelationships.

## SUMMARY AND CONCLUSIONS

There is considerable evidence that Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma represent variations of a basic disorder of the reticuloendothelial system. Letterer-Siwe disease, since it is rapidly fatal, usually does not show the lipidization of

the lesions seen in the more protracted Schüller-Christian disease. Eosinophilic granuloma of bone shows lesions which clinically, roentgenologically and histologically cannot be distinguished from comparable lesions in Letterer-Siwe or Schüller-Christian disease.

The absence of lipophagic foam cells in many of the lesions of Schüller-Christian disease, especially those of short duration, and the fact that lipemia is hardly more constant in Schüller-Christian disease than in certain other types of reticuloendotheliosis cast doubt on the correctness of considering Schüller-Christian disease as a primary disturbance of lipid metabolism.

Although at present it is impossible to draw conclusions concerning cutaneous eosinophilic granuloma, it would seem logical, because of the histologic similarity, tentatively to group this condition with the others under discussion.

The cutaneous manifestations of the systemic reticuloendothelial granulomas are subject to considerable variation. In the Letterer-Siwe type there is a noteworthy tendency to cutaneous hemorrhage. Necrotic oral lesions have also been reported. In the Schüller-Christian type the commonest eruptions are the diffuse papular or seborrhealike types. In our 2 cases the eruptions simulated keratosis follicularis. Eosinophilic granuloma of the skin is characterized by nodules, plaques or tumefactions, which may be smooth, ulcerated or verrucous and may be located on various parts of the body.

# PEMPHIGUS VULGARIS

## A Clinicoanatomic Study

BEATRICE H. KUHN, M.D.
CHARLESTON, W. VA.

AND

LALLA IVERSON, M.D.
DURHAM, N. C.

THE TERM pemphigus is applied to a group of relapsing, usually fatal, bullous eruptions. The cause of pemphigus vulgaris remains obscure, and no specific treatment is known to be uniformly effective.

Recently much discussion has centered on the role of the adrenal gland in pemphigus, together with the associated characteristic electrolyte pattern and the fluid balance,[1] the results of adrenal cortex replacement therapy[2] and the anatomic changes seen in the adrenal gland on postmortem examination.[3] Since little attention has been directed to complete postmortem studies, the following 4 cases are reported as a contribution to the total knowledge concerning pemphigus vulgaris.

### REPORT OF CASES

*Case* 1.—T. O. M., a 38 year old white male truck driver, was admitted to the hospital complaining of a "sore mouth and body rash of thirteen months' duration." He was seen by his physician at the onset of his present illness; a diagnosis of Vincent's infection of the mouth was made, and appropriate treatment was instituted. During the ensuing thirteen months he had numerous exacerbations characterized by sore gums and a sore mouth, associated with a generalized chronic papulovesicular eruption. Examination showed an asthenic lethargic white man

From the Department of Dermatology, Duke Hospital, and the Department of Pathology, Duke University School of Medicine, Durham, N. C.

1. Talbott, J. H.; Lever, W. F., and Consolario, W. V.: Metabolic Studies on Patients with Pemphigus, J. Invest. Dermat. **3**:31, 1940.

2. Lever, W. F., and Talbott, J. H.: Pemphigus: A Further Report on Chemical Studies of the Blood Serum and Treatment with Adrenocortical Extract, Dihydrotachysterol or Vitamin D, New England J. Med. **231**:44, 1944.

3. Goldzieher, J. W.: The Adrenal Glands in Pemphigus Vulgaris: Report of Six Autopsies and Review of Literature, Arch. Dermat. & Syph. **52**:369 (Nov.-Dec.) 1945; The Adrenal Glands in Pemphigus Vulgaris: Report of a Case, ibid. **53**:42 (Jan.) 1946. Grace, A. W., and Hellman, D. L.: Pemphigus Vulgaris: Successful Results Following Transfusion of Blood from Persons Who Have Recovered from the Disease, ibid. **53**:249 (March) 1946.

with a generalized eruption consisting of multiple pustules, vesicles and pigmented macules with extensive crusting. The patient had a definite musty odor. The oral mucosa, buccal mucosa and tongue were edematous and erythematous. Staphylococcus aureus and Staphylococcus albus were cultured from the cutaneous lesions.

While in the hospital the patient received numerous blood transfusions and local treatment, without effect. His condition was essentially unchanged for eight weeks, after which he had a daily elevation of temperature varying from 38 C. (100.4 F.) to 39 C. (102.2 F.). He became rapidly worse, and he died approximately three months after the onset of his illness. The final diagnosis was chronic pemphigus.

*Postmortem Observations.*—The body was that of a thin white man. Microscopic sections of the skin revealed a pronounced change in the lower portion of the prickle cell layer. Intercellular edema, where it was great, was accompanied with separation of the epidermis and vesicular formation. The underlying corium showed a slight infiltration of lymphocytes, plasma cells, monocytes, and occasional polymorphonuclear cells. The tonsils were grayish, and the crypts were filled with green purulent material. There were superficial small patches of necrosis in the pharynx and trachea. The lungs showed lobular pneumonia on the left and a partially calcified apical scar on the right. A few pleural adhesions were seen posterior to the diseased right apex. There were no alterations of the heart, liver, spleen or other viscera. The testicles were atrophied, showing a decrease in Leydig's cells, aspermia and an increase in interstitial connective tissue. The combined weight of the adrenal glands was 30 Gm. There was an increase in connective tissue of the capsule, the zona glomerulosa and the upper part of the zona fasciculata. There was no depletion in lipid content, no necrosis and no nodular cortical hyperplasia.

*Case* 2.—W. N. M., a 43 year old white farmer, was first admitted to the hospital with a recurrent vesicular eruption of two months' duration. He had received nonspecific therapy, without relief, from his local physician. On examination the skin showed a generalized vesicular eruption with decided secondary infection and crusting. Nikolsky's sign was positive. The phytopharmacologic index was 46 per cent. During his hospitalization the patient was given 1 Gm. of suramin sodium (germanin) intravenously daily for five days. He was discharged after three weeks of hospitalization with complete clinical remission.

He continued well for two years, at which time an extensive vesicular eruption developed. He was seen in the outpatient clinic three months later. At this time his plasma chlorides were 560 mg. per hundred cubic centimeters. The phytopharmacologic index was 63 per cent. Five months after the development of his second eruption he was readmitted to the hospital for treatment with suramin sodium. He had received the usual local treatment and accessory vitamin preparations at home, without relief. Examination at this time showed a generalized bullous eruption with secondary infection and crusting. The plasma chlorides were reported as 584 mg., serum calcium 10.1 mg. and serum phosphorus 2.6 mg. per hundred cubic centimeters; serum sodium was 137.3 equivalents per liter and serum potassium 4.1 equivalents per liter. During this hospitalization he was given 8 Gm. of suramin sodium without improvement, but he subsequently responded to large doses of a vitamin D preparation, and multiple small blood transfusions. He was discharged two months later, much improved.

Two months after discharge the patient was admitted for the third and last time with an acute generalized exacerbation of all his previous signs and symptoms. These were of three weeks' duration. Examination at this time showed patchy erythema of the skin with a generalized bullous eruption. The patient received 5 mg. of desoxycorticosterone acetate and a blood transfusion, without improvement. During his three weeks of hospitalization the patient showed signs of progressive

deterioration, with loss of weight, anorexia and a daily elevation of temperature. His death, three years after onset of the first symptoms, terminated his third admission. The final diagnosis was pemphigus vulgaris.

*Postmortem Observations.*—Twenty-five per cent of the body curface was covered with foul-smelling ulcers. The earliest microscopic changes noted in the skin were in the lower cells of the prickle cell layer. Intercellular bridges were lost, and the nuclei were pyknotic. The cytoplasm was more eosinophilic than that usually seen and occasionally contained pink-staining granular inclusions. Intercellular edema was prominent, and, where alterations in epithelial cells were most decided, there was separation of the layers of the epidermis by serum, fibrin and infiltration with inflammatory cells, including large numbers of polymorphonuclear cells and eosinophils. It is of interest that the corium showed a more decided inflammatory reaction in the regions of vesicular formation than in areas of early epithelial change. Some of the cutaneous sections showed an exposed pars papillaris covered only by a thin germinal layer of epidermal cells. In these sections the corium was edematous. The sinusoids of the superficial lymph nodes were filled with inflammatory cells and necrotic debris. Necrosis of some of the lymphoid follicles was noted. The lungs showed a few calcified scars accompanied with pleural adhesions. The other viscera were remarkably free of outstanding changes. The stomach mucosa was congested and inflamed; several small ulcers were present. The sinusoids of the liver were dilated and infiltrated with polymorphonuclear cells. There were hyperplasia and occasional necrosis of the malpighian follicles in the spleen. Adhesions, crescent formation and hyaline thickening of the basement membrane characterized some of the renal glomeruli. There was atrophy of both testicles. The adrenal glands weighed 4 Gm. each. There was increased thickness of the capsule. Local areas of necrosis accompanied with lymphoid infiltration were noted. There was decided depletion of fat in the zona fasciculata. Nodular hyperplasia of the zona glomerulosa was prominent.

*Case* 3.—S. M. W., a 28 year old Negro housewife, was admitted with a history of a generalized vesicular eruption of one month's duration. Examination showed a generalized bullous eruption of the skin with secondary infection, crusting and desquamation. The hemoglobin was 50.4 per cent and the white blood cell count 12,480 per cubic millimeter. Serum chlorides were reported as 520 mg. per hundred cubic centimeters. The patient received multiple small transfusions, "pentnucleotide" (the sodium salts of the pentose nucleotides from the ribonucleic acid of yeast), 400,000 units of penicillin intramuscularly, sulfadiazine by mouth and 5 cc. of adrenal cortex extract. The white blood cell count was decidedly diminished (reported as 2,520 per cubic millimeter) during the latter part of her hospitalization, five days before her death. The leukocyte count dropped to 240 per cubic milimeter the day before her death. The patient died one month after admission. The final diagnosis was pemphigus vulgaris.

*Postmortem Observations.*—The important observations were limited to the skin, mucous membranes and bone. The cutaneous lesions resembled those of the patient in case 2. There was decided necrotizing ulceration of the trachea and bronchus, with desquamation of epithelium and scattered areas of submucosal hemorrhagic necrosis and edema. The lungs showed patchy hemorrhage and edema, which in some areas was associated with hyaline changes of the small vessels. About 200 cc. of clear fluid was observed in each pleural cavity. The esophagus showed small necrotizing ulcers, and the cardiac end of the stomach contained a 3 by 5 cm. ulcer. The surfaces of these ulcers were characterized microscopically by thick layers of serum and fibrin, hemorrhage, occasional hyaline arterioles and conspicuous absence of inflammatory cells. The latter was attributed to the absence of myelopoiesis in the bone marrow. The liver weighed 2,820 Gm. and exhibited

central lobular necrosis, accompanied with fatty alteration of parenchymal cells. No vascular changes were seen. "Regeneration" of the bile ducts and cords was noted in some periportal areas. Beginning atrophic changes were seen in the ovaries and breasts. The adrenal glands weighed 20 Gm. and showed increase in thickness of the capsule and increase in interstitial connective tissue. The decided interstitial edema was accentuated by the depletion of fat in the zona fasciculata. Areas of cortical hyperplasia and one or two tiny foci of early necrosis were seen. The reticularis was hemorrhagic. No lymphocytic reaction was noted.

*Case* 4.—A. C., a 56 year old white housewife, was first admitted to the hospital with a painless vesicular eruption of six months' duration. Physical examination showed a generalized hemorrhagic vesicular eruption, with secondary infection and some scar formation. The phytopharmacologic index was 65 per cent. Biopsy of the skin showed a microscopic picture compatible with pemphigus vulgaris. The patient was hospitalized for three and one half weeks, receiving local treatment as indicated, adequate diet and accessory vitamins. She was discharged unimproved.

Following discharge, the patient was treated by her family physician with large doses of vitamin preparation and bismuth and arsenic compounds. She continued to lead a normal life until three weeks before her second admission, at which time she was treated with radon seed implantation for carcinoma of the right cheek. An acute generalized exacerbation of her previous signs and symptoms developed. Examination at this time showed a generalized bullous eruption, with decided secondary infection and ulceration. Serum chlorides were reported as 628 mg. per hundred cubic centimeters. She received local treatment for her skin, without improvement, but continued essentially unchanged until four days before death, at which time she became irrational and had a high irregular fever. She died nine months after the onset of the first symptoms. The final clinical impression was pemphigus vulgaris.

*Postmortem Observations.*—The skin was covered with a sloughing bullous eruption. The histologic appearance was consistent with the diagnosis of pemphigus vulgaris. Intraepidermal vesiclular formation, ulceration and secondary infection were prominent. A few adhesions were present in both abdominal and thoracic cavities. The heart weighed only 350 Gm., in spite of excess deposits of fat. The tongue and buccal mucosa showed numerous ulcers with irregular borders. Microscopically the tongue showed decided superficial necrosis and swelling of the lowermost prickle cells. In the mucosa of the urinary bladder was a necrotic ulcer of 2 cm. There was an ovarian cyst on the right side and a small colloid adenoma of the thyroid. The adrenal glands weighed approximately 20 Gm. The capsule was of normal thickness. There was a relative increase in interstitial connective tissue, probably related to the decrease in fat content of the cells comprising the zona fasciculata. There was a diffuse and focal infiltration of lymphocytes in the lower part of the cortex. One or two small areas of necrosis were seen. In the zona glomerulosa were several clumps of large hyperplasic cells, and in the capsule were a few nodules of cortical cells.

## COMMENT

In approximately 300,000 patients who have been seen at Duke Hospital the diagnosis of pemphigus has been made sixty-four times. This figure includes all clinically recognized types of the disease. Of the 64 patients, 5 have been followed to the time of death in this clinic. The duration of the disease in the 4 cases herein summarized was two to thirty-six months, an average of seventeen months from the

first appearance of clinical signs or symptoms to the death of the patient. Three of these 4 patients were white, and 1 was Negro. There were 2 men and 2 women, with ages ranging from 28 to 56 years.

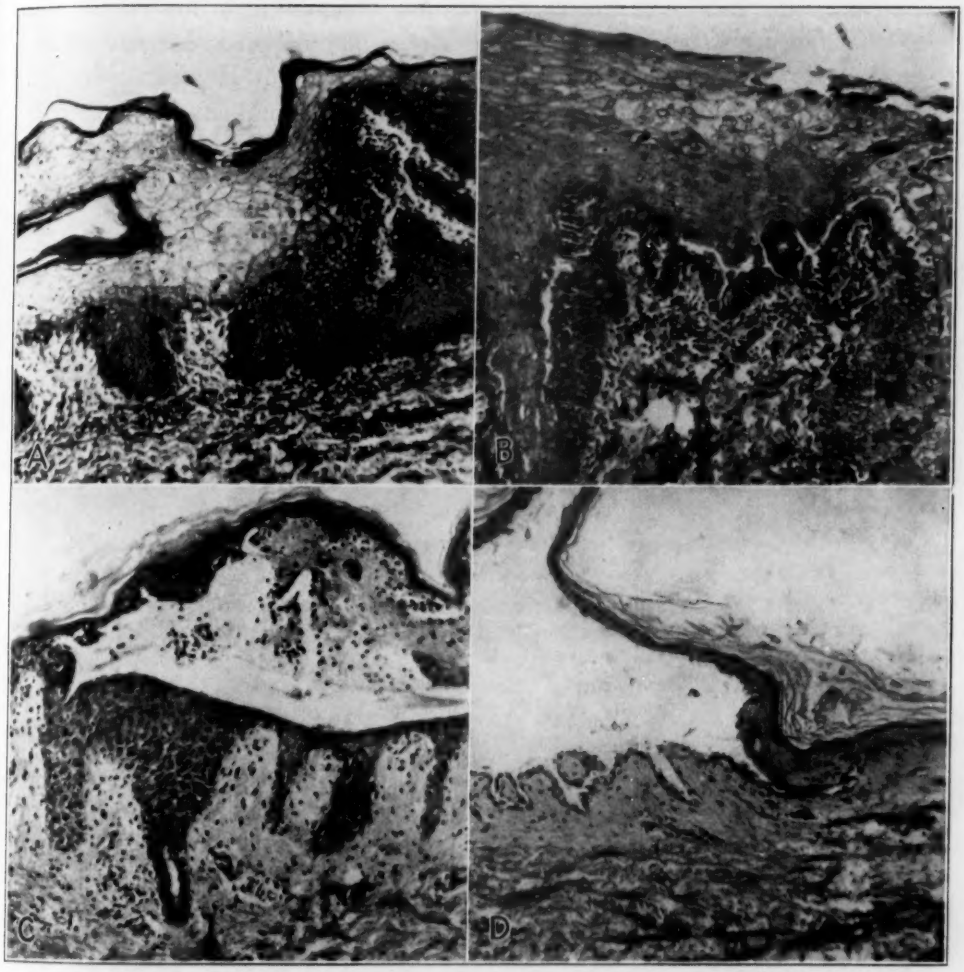



Fig. 1.—Pemphigus vulgaris, primary lesion. *A* (case 3), skin. Swelling of epidermal cells previous to vesicular formation, showing the inflammatory reaction in the corium (Masson trichrome strain). *B* (case 4), tongue. This is an early reaction in the mucous membrane similar to that seen in the skin (*A*). The swelling of epithelial cells and beginning vesicular formation are apparent. Extensive ulceration eventually accompanies this reaction (hematoxylin and eosin stain). *C* (case 2), skin. This typical intraepidermal vesicle contains serum, fibrin, polymorphonulclear neutrophils, lymphocytes and some large mononuclear cells. The edema of the pars papillaris and the perivascular mononuclear reaction are apparent (hematoxylin and eosin stain). *D* (case 1), skin. An older vesicle in chronic pemphigus, showing atrophy of the epidermis, absence of decided inflammation and the intraepidermal bleb. Other sections show exposed papillary projections covered by a thin layer of germinal epithelium, as seen at the floor of the vesicle.

We have used, alone and in combination, repeated small transfusions, large doses of vitamin preparations, sulfonamide drugs, penicillin, adrenal cortex extract, convalescent serum, suramin sodium ("germanin"), iron cacodylate and coagulin. We have not been impressed by the superiority of any single preparation or combination of therapeutic measures. Our patients have not presented any atypical observations, and, in general, the disease has followed the classical clinical pattern from the onset to death.

In all 4 cases typical lesions of the skin and oral mucous membranes constituted the outstanding evidence of the primary disease process. The earliest change in the skin consisted of a swelling of the epthelial cells in the prickle cell layer, loss of intercellular bridges and formation of small red granular bodies within the swollen eosinophilic cytoplasm of the prickle cells. These observations are suggestive of a primary viral causation of pemphigus vulgaris. The vesicles and inflammatory reaction appear secondary to the change described.

The lesions on the buccal mucosa and tongue tend to ulcerate and become necrotic more rapidly than those on the skin. Necrotizing ulcerative lesions of other mucosal surfaces were noted in all cases. The changes were most apparent in case 3, because of associated granulocytopenia. These observations corroborated those of Lever and Talbott,[4] who observed a tendency to generalized mucous membrane involvement in patients with combined oral and cutaneous lesions of pemphigus. Whether the former changes represent primary or secondary effect is not known.

Anatomic alterations of the other viscera were varied. In general, nonspecific changes were noted, which may have resulted from metabolic derangement, from the high temperature occurring terminally or from circulating bacteria (or their toxins) due to secondary infection of the cutaneous lesions. These nonspecific changes are classified as follows:

1. *Focal Injuries Occurring in the Liver, Kidneys and Adrenal Glands.*—In case 3, decided central lobular necrosis of the liver, accompanied with fatty alteration, was noted. Gellis and Glass[5] also described fatty alteration of the liver, and Eller and Kest[6] reported hepatomegaly. In our case the associated reaction to treatment with

4. Lever, W. F., and Talbott, J. H.: Pemphigus: A Clinical Analysis and Follow-Up Study of Sixty-Two Patients, Arch. Dermat. & Syph. **46**:348 (Sept.) 1942.

5. Gellis, S., and Glass, F. A.: Pemphigus: A Survey of One Hundred and Seventy Patients Admitted to Bellevue Hospital from 1911 to 1941, Arch. Dermat. & Syph. **44**:321 (Sept.) 1941.

6. Eller, J. A., and Kest, L. H.: Pemphigus: Report of Seventy-Seven Cases, Arch. Dermat. & Syph. **44**:337 (Sept.) 1941.

sulfonamide drugs must be considered as a major factor in the production of the necrosis of the liver. However, slight central necrosis was noted in case 4, in which sensitivity phenomena were not clinically evident. In cases 2 and 4 there was also shown serous hepatitis, probable evidence of circulating inflammatory agents.

In 1 of the cases previously reportd,[5] the kidneys were swollen and the condition resembled acute glomerulonephritis. In case 2 of our series many of the renal glomeruli showed thickening of the base-

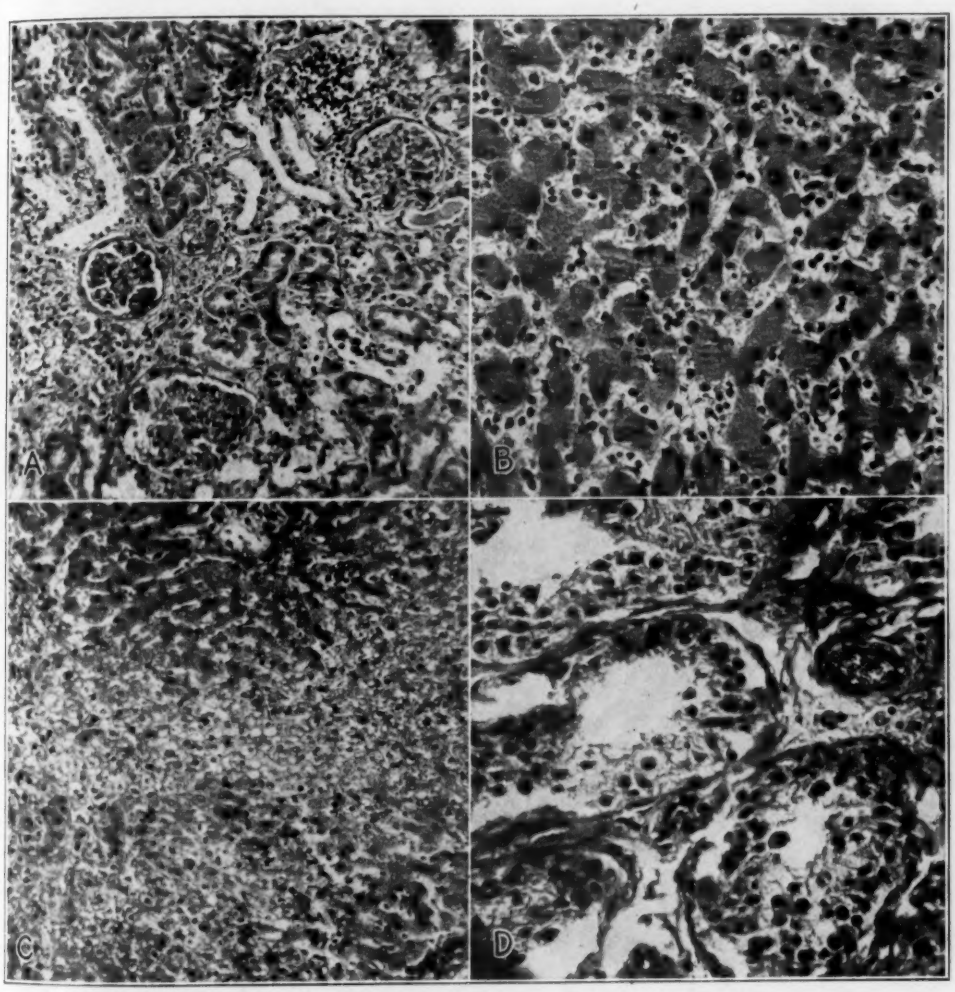



Fig. 2.—Pemphigus vulgaris, secondary lesions. *A* (case 2), kidney, with thickening of the capsule and basement membrane, swelling of the glomerular tuft, capsular engorgement, outpouring of fibrin into the capsular space and interstitial inflammation (hematoxylin and eosin stain). *B* (case 2), liver. Diffuse infiltration of hepatic sinusoids by polymorphonuclear neutrophils is evident (hematoxylin and eosin stain). *C* (case 3), liver, showing the central necrosis and fatty alteration of the parenchymal cells (hematoxylin and eosin stain). *D* (case 2), testis. This shows aspermia and beginning atrophy (hematoxylin and eosin stain).

ment membrane, capsular adhesions and early epithelial crescent formation. Some hemorrhage into glomerular spaces occurred. The changes in the lymph nodes and the acute splenic tumor support the interpretation of the renal lesions as the result not of the primary disease process but of superimposed infection.

The changes in the adrenal glands have been herein emphasized. Case 1 illustrates the observations of Talbott, Lever and Consolazio[1] concerning the mild changes in the adrenal glands in patients with

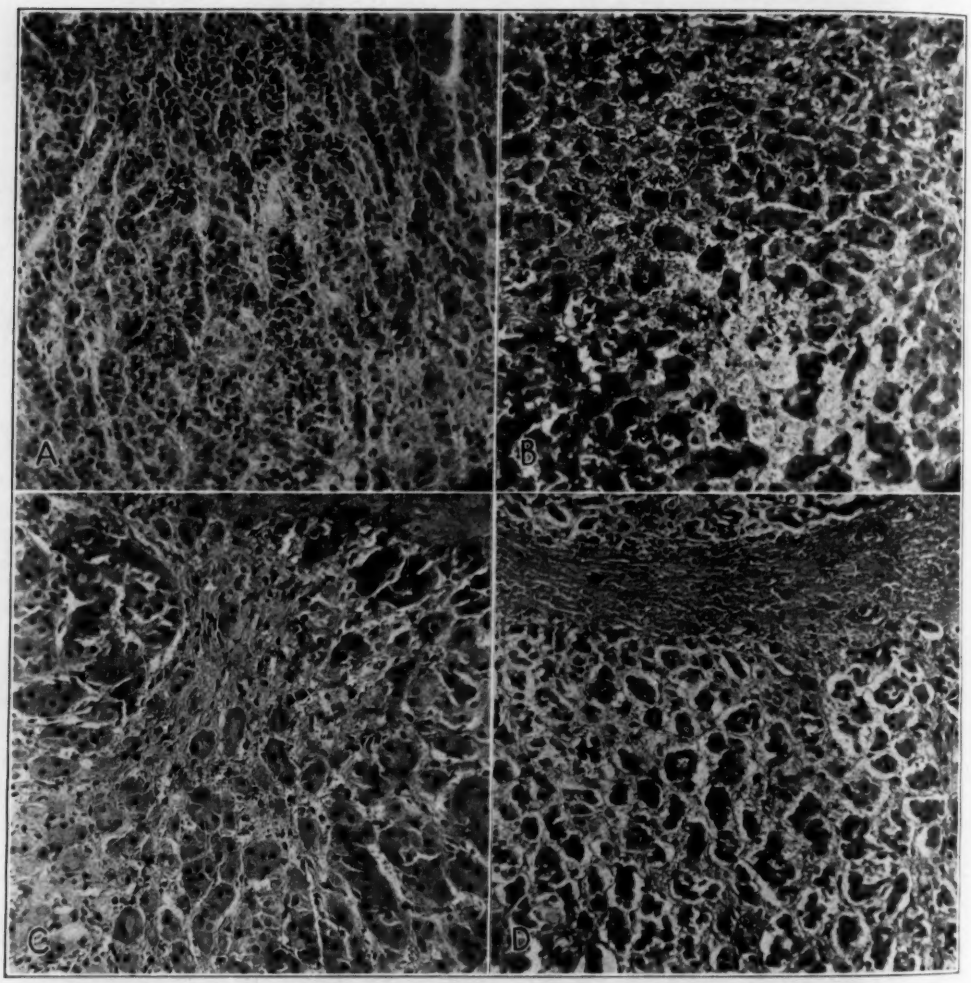



Fig. 3.—Pemphigus vulgaris, secondary lesion. *A* (case 1), adrenal gland. There is slight thickening of the capsule, moderate loss of lipid and an apparent increase in interstitial connective tissue (hematoxylin and eosin stain). *B* (case 2), adrenal gland, showing loss of lipid, focal necrosis of cortical cells and lymphocytic reaction (hematoxylin and eosin stain). *C* (case 2), adrenal gland. This area shows beginning repair of the injured cortex by connective tissue. *D* (case 3), adrenal gland, showing the thickened capsule and cortical "regeneration" (seen also in the adrenal gland in case 4). There is some necrosis of cortical cells, but the nuclei of many cells are still well preserved (hematoxylin and eosin stain).

chronic pemphigus. The alterations in these glands in the other 3 cases were not dramatic and are similar to those which are often seen secondary to numerous disease processes other than pemphigus. Goldzieher's cases[3] present changes which are more pronounced and diffuse, but which are qualitatively similar to those in our series. These changes consist of loss of lipid, necrosis of cortical cells, lymphocytic infiltration, fibrosis and nodular regeneration. When the injury is more prominent than in our cases, it is conceivable that functional alterations will occur. It is interesting that 2 of the patients of this series (cases 2 and 3) received adrenal cortex preparations with no improvement. However, it must be strongly emphasized that attention not be directed exclusively to the adrenal glands. To limit the scope of clinical and anatomic studies in such a way will postpone the final understanding of the pathogenesis of this disease.

2. *Diffuse Atrophy of the Gonads.*—Decided and moderate testicular atrophy occurred in the 2 men; ovarian atrophy with associated involution of mammary glandular tissue was indicated in case 3. Similar changes in the gonads are common in other chronic illnesses.

3. *Necrosis of the Small Arterioles.*—This change accompanied the focal injuries noted in the liver, kidney and adrenal glands and the necrotizing ulcerations of the mucous membranes. The arteriolonecrosis was not extensive enough to be interpreted as responsible for the latter lesions.

## SUMMARY AND CONCLUSIONS

Four cases of pemphigus vulgaris, with postmortem observations are presented.

No specific therapeutic agent has been observed to be of special value in the treatment of pemphigus vulgaris.

The major observations at autopsy were limited to the skin and mucous membranes, evidence of the primary disease process. Visceral reactions were secondary, grouped as follows: focal lesions occurring in the liver, kidneys and adrenal glands and diffuse atrophy of the gonads. Both primary and secondary lesions may be accompanied with arteriolonecrosis.

Changes in the adrenal gland in cases of pemphigus vulgaris are not of sufficient magnitude to justify new concepts of treatment and pathogenesis on the basis of functional alterations of this organ.

1109 Quarrier Street.

# AMBULATORY TREATMENT OF EARLY SYPHILIS

## An Experimental Study with Report of Injection of Penicillin in Water-in-Oil Emulsion

ALFRED COHN, M.D.
THEODORE ROSENTHAL, M.D.
AND
ISAAK GRUNSTEIN, M.D.
NEW YORK

THIS report deals with various instructive observations recorded in the course of an experimental study of ambulatory treatment of patients with early syphilis with penicillin in water-in-oil emulsion. The commercial production of the original oily vehicle designed for retarding absorption and excretion and used in this investigation[1] has already been replaced by some others, which, however, also employ the same fundamental principles first reported by Freund and Thomson.[2] Nevertheless, it is hoped that the therapeutic response observed with this type of treatment will promote further research in this direction and also stimulate the investigation of other problems encountered in this study. Our results, therefore, are not intended to present a schedule for routine treatment. What follows is merely a pilot study, which may be used as a guide to a further approach to this problem.

### METHOD OF TREATMENT

The use of a single intramuscular injection of sodium penicillin in water-in-oil emulsion yielded satisfactory results in the treatment of gonococcic infections.[3] This method, therefore, suggested itself for

---

From the Division of Venereal Disease Research (Dr. Cohn and Dr. Grunstein) and the Bureau of Social Hygiene (Dr. Rosenthal), Department of Health, New York.

1. The oily vehicle used in this study was "pendil" (a mixture of cholesterol derivatives and peanut oil), made available to us by Endo Products, Inc., New York.

2. Freund, J., and Thomson, K. J.: A Simple Rapid Technic of Preparing Water-in-Oil Emulsion of Penicillin, Drugs & Biol. Sc. **101**:468 (May) 1945.

3. Cohn, A.; Kornblith, B. A.; Grunstein, I.; Freund, J., and Thomson, K. J.: Treatment of Gonorrhea with Penicillin: Results of Therapy with Penicillin in

the treatment of patients with early syphilis. Immediate therapeutic results observed early in this study were promising and were reported in a previous publication.[4]

The present report covers a period of twenty-six months, from March 1945 to June 1947. A total of 96 patients with syphilis (94 men—24 white and 70 Negro and 2 women—both Negro) were treated; 3 were being retreated because of failure to respond to previous treatment with penicillin. The total group of 96 patients consisted of: 16 patients with seronegative primary syphilis, 39 patients with seropositive primary syphilis and 41 patients with secondary syphilis.

To date 66 patients have been followed up from three to twenty-six months.

Various treatment schedules were used: In the majority of cases (84) one intramuscular injection was administered every twenty-four hours; 12 patients received their daily dosage in two equally divided doses at twelve hour intervals. Total dosages of 2,000,000 units up to 5,000,000 units of sodium penicillin in water-in-oil emulsion were used. The daily dose varied from 400,000 to 1,000,000 units. The total treatment period of 83 patients was five days, while 13 patients were treated over a period of ten days. At the onset of the study the daily dose of sodium penicillin was given in 9 cc. of the water-in-oil emulsion; later, the total amount of the emulsion was reduced to 4.5 cc., thus lessening the local discomfort caused by the injection of the larger amount. Several brands of penicillin were used. Details of the preparation of single doses for office use or of larger quantities of sodium penicillin in water-in-oil emulsion for clinical or hospital use have been described previously.[5]

Before treatment was started all patients were examined clinically by dark field examination (with rare exceptions) and serologically by a battery of tests such as the titrated Wassermann test used in New York; which was later replaced by the Kolmer test, and the diagnostic Kline, diagnostic Kahn and Mazzini flocculation tests.[6]

---

Water-in-Oil Emulsion as Compared with Those Obtained by Single or Multiple Injections of Aqueous Penicillin Solutions, J. Ven. Dis. Inform. **27**:154-159 (June) 1946.

4. Cohn, A.; Rosenthal, T., and Grunstein, I.: Repository Injection of Penicillin in Water-in-Oil Emulsion: Effect on Early Syphilis; Preliminary Report, Bull. New York Acad. Med. **22**:478 (Sept.) 1946.

5. Cohn, A.; Kornblith, B. A.; Grunstein, I.; Thomson, K. J., and Freund, J.: Repository Injection of Penicillin in Water-in-Oil Emulsion. Effect on Gonorrhea, Proc. Soc. Exper. Biol. & Med. **59**:145-147 (June) 1945.

6. Miss Agnes C. Haman of the Bureau of Laboratories, Department of Health, New York, performed the serologic tests.

At the beginning of the study, 56 patients were hospitalized for a period of five or ten days, respectively, while, later, treatment was given ambulatorily to 40 patients. Reexaminations were made at weekly intervals during the first month following treatment, at monthly intervals during the following three months and later at three month and six month intervals. After six months, as a rule, an examination of the spinal fluid was made.

## RESULTS

Dark field examinations, which originally yielded positive results for Treponema pallidum, yielded negative results when made twenty-four hours after the beginning of treatment in 25 cases. One patient presented positive results in dark field examination at this time, but showed negative results when reexamined twenty-four hours later.

*Clinical Diagnosis, Period of Observation and Therapeutic Results Obtained in a Group of 66 Patients with Early Syphilis Treated with Sodium Penicillin in Water-in-Oil Emulsion*

| Period of Observation (in Months) | Clinical Diagnosis of Syphilis | Total No. of Patients | Progress Satisfactory | Infectious Relapse (Period) | Serologic Relapse (Period) | Persistently Positive Serologic Reaction (Period) |
|---|---|---|---|---|---|---|
| 3 to 6 | Seronegative primary<br>Seropositive primary<br>Secondary | 4<br>11<br>4 | 3<br>10<br>1 | 1 (3 mo.)<br>1 (2 mo.)<br>1 (3 mo.)<br>1 (6 mo.)<br>1 (5 mo.) | | |
| 7 to 12 | Seronegative primary<br>Seropositive primary<br>Secondary | 4<br>12<br>14 | 3<br>11<br>12 | <br><br>1 (8 mo.) | 1 (6 mo.)<br><br> | <br>1 (11 mo.)<br>1 (6 mo.) |
| 13 to 18 | Seronegative primary<br>Seropositive primary<br>Secondary | 3<br>2<br>5 | 3<br>2<br>4 | <br><br> | <br><br>1 (11 mo.) | <br><br> |
| 19 to 23 | Seronegative primary<br>Seropositive primary<br>Secondary | 0<br>3<br>3 | —<br>2<br>3 | <br>1 (22 mo.)<br> | <br><br> | <br><br> |
| 24 to 36 | Seronegative primary<br>Seropositive primary<br>Secondary | 1<br>0<br>0 | 1<br>—<br>— | <br><br> | <br><br> | <br><br> |
| Total | | 66 | 55 | 7 | 2 | 2 |

Complete healing of the primary lesions took place within an average period of twelve and two-tenths days (minimum three days and maximum thirty-seven days). Complete involution of the secondary lesions occurred within an average period of seventeen and eight-tenths days (minimum three days and maximum one hundred and twenty days). The involution period depended, of course, on the size and character of the lesions. The actual time of involution of lesions in individual cases might have been shorter than reported, because some of the patients did not return for reexamination on the date requested.

The table shows the clinical diagnosis and the therapeutic results for the 66 patients who were under observation for a period of three to twenty-six months.

Among the 66 patients there were 7 with clinical relapse and 2 with serologic relapse. Two additional patients presented a persistently positive Wassermann reaction, without any change in titer over a period of six and eleven months, respectively.

Clinical relapse in 3 patients, 1 with seronegative and 2 with seropositive primary syphilis, were observed, in 2 within a period of three months and in the third after twenty-two months. Clinical relapse in 4 patients with early secondary syphilitic lesions appeared three, five, six and eight months, respectively, after the termination of treatment. All the cases of clinical relapse were confirmed by dark field examination.

The clinical relapse of the patient with seronegative primary syphilis was observed three months after treatment, while his serologic reaction was still negative. This patient was promptly retreated with penicillin. The complement fixation reaction of 1 patient with seropositive primary syphilis was negative at the time of his clinical relapse, but was associated with weekly positive reactions to flocculation tests, while in the second case positive serologic reactions persisted during the twenty-two months of observation. A serologic pattern of a negative reaction to a complement fixation test, but accompanied with a positive reaction to a flocculation test, was observed for 1 of the 4 patients with secondary syphilis at the time of his clinical relapse.

The possibility of reinfection instead of relapse cannot be entirely excluded in 2 patients. However, since the rigid criteria of reinfection were not satisfied, they were classified as presenting relapse.

As to the serologic results in general, the 12 patients with seronegative primary syphilis showed persistently negative serologic reactions over a varying period of three to twenty-six months, atlhough 1 of them presented clinical relapse three months after treatment, as mentioned previously.

In the second group of 28 cases of seropositive primary syphilis, the positive serologic reactions of 26 patients became negative within an average period of three and five-tenths months (minimum eighteen days and maximum nine months). The serums of 2 other patients, however, retained their high positive titer during an observation period of eleven and twenty-one months, respectively, without any signs of clinical relapse in the first case; in the second case there was secondary relapse at the end of twenty-one months. The spinal fluid of both patients, 1 of whom was examined seven months and the other ten months following treatment, was observed to be normal.

Among the group of 26 patients with secondary syphilis, the serologic reaction of 16 (2 retreated because of clinical relapse) became negative in an average of seven months (minimum two months and maximum sixteen months); one of them presented serologic relapse eight months after treatment. The serums of another 7 patients showed a gradual decrease of serologic titer within a period of three to fourteen months. Two of these had a clinical relapse three and five months, respectively, after treatment. Finally, 3 patients presented persistently positive serologic reactions over a period of six to eight months; 2 of them presented clinical relapse.

The examination of the spinal fluid of 49 patients was performed approximately six months after termination of treatment. Protein determination, cell counts, complement fixation tests and tests with colloidal gold were made of each specimen. The results obtained were negative except in 3 patients. Two of them showed an increase of lymphocytes (5 and 8 cells, respectively); the corresponding serologic reactions of the blood and the spinal fluid were negative. The spinal fluid of a third patient, who had a persistently positive serologic reaction for a period of six months, also showed a positive serologic reaction.

The incidence of clinical and serologic relapses or persistently positive serologic reactions in 11 patients was apparently independent of the various treatment schedules used. However, relapse occurred in 10 patients who were given single daily injections of penicillin; the eleventh patient received two injections daily. Relapse occurred in 1 patient after a total dosage of 2,000,000 units had been administered; relapse occurred in 2 patients after a total dosage of 4,200,000 units and in 5 other patients after 5,000,000 units of sodium penicillin in water-in-oil emulsion, given over a period of five days. Relapse occurred in 2 other patients after 5,000,000 units had been given over a period of ten days. Relapse was exhibited in the eleventh patient after a total dosage of 5,000,000 units had been administered in two daily injections over a period of five days.

As to the side effects of sodium penicillin in water-in-oil emulsion, it can be stated that no local or systemic reactions of a severe nature were encountered. The majority of patients complained of transitory pain, radiating from the site of injection to the lower limb, and showed a Herxheimer reaction of a mild degree following the first or second injection of penicillin. Four patients experienced a transitory urticarial or erythema-like eruption during or shortly following treatment. It was also observed that 3 Negro patients showed a pityriasis rosea-like eruption within a period of two to three weeks after termination of treatment. Whether or not the pityriasis rosea-like eruption should be considered as an allergic reaction to penicillin or

to the constituents of the emulsifying vehicle or whether it was purely coincidental was not determined.

It has been observed by us that levels of penicillin in the serum, determined at identical intervals during a twenty-four hour observation period, showed decided fluctuation in the same patient and in different patients, even if the same specimens were tested simultaneously in two different laboratories. Nevertheless, despite fluctuations and frequent complete absence of penicillin in the serum during the second half of the twenty-four hour period after treatment, the therapeutic response was satisfactory in 55 out of 66 patients observed for a prolonged period.

In order to investigate this apparent paradox, it was considered desirable to compare penicillin absorption and excretion when the drug was administered in isotonic solution of sodium chloride or in an oily vehicle in the same patient. Three groups, of 2 patients each, were given single injections of penicillin in watery solution, with doses of 150,000, 500,000 and 1,000,000 units, respectively. Five days later the same groups received the identical doses of penicillin in water-in-oil emulsion, in single injections. In this series of tests there was no essential difference in the duration or height of levels of penicillin in the serum in the two groups receving penicilln in water alone or in water-in-oil emulsion. However, the twenty-four hour levels of penicillin in the urine of patients who received single injections of water-in-oil emulsion were twenty to one thousand times higher than the levels of penicillin in the urine of the patients receiving single injections of identical amounts of penicillin in water alone, even if no penicillin was detectable in the serum in either group at this time, i.e., twenty-four hours after injection.[7]

There is also clinical evidence for the therapeutic superiority of penicillin in the oily vehicle, even if the number of patients treated with penicillin in isotonic soluton of sodum chlorde alone is limited, for obvious reasons. Two patients with early syphilis received total dosages of 2,000,000 and 4,200,000 units, respectively, of sodium penicillin in isotonic solution of sodium chloride over a period of five days. The single intramuscular injections were administered at twenty-four hour intervals. Relapse occurred in both patients within two to three months.

## COMMENT

All these observations, correlated with therapeutic results, indicate that the administration of penicillin in water-in-oil emulsion prolongs the presence and probably the therapeutic action of the anti-

7. Mrs. Carolyn R. Falk, Bureau of Laboratories, Department of Health, New York, made the determination of levels of penicillin in the blood and the urine.

biotic agent within the body beyond the time when assayable levels of penicillin in the serum are demonstrable. These observations corroborated the observation of Jawetz,[8] who demonstrated in experiments with animals that the action of penicillin apparently persists after disappearance of the drug from the blood stream.

The therapeutic results obtained thus far in this study indicate the feasibility of ambulatory treatment of patients with syphilis with penicillin in an oily vehicle. Because of the experimental nature of this study and because of the limited number of patients observed, for a relatively short period of time, no definite schedule for the ambulatory treatment of early syphilis with penicillin can be offered at present. Our current limited knowledge as to the most efficient fractions or constituents of penicillin for the treatment of syphilis requires, per se, additional detailed investigation. Progress in this direction together with improvement of the vehicle, and the determination of the proper time-dose ratio must be made before any optimal treatment schedule can be recommended.

## SUMMARY

A total of 96 patients with early syphilis (56 hospitalized and 40 ambulatory) were treated with varying amounts of penicillin in water-in-oil emulsion, total dosages ranging from 2,000,000 to 5,000,000 units, over a period of five or ten days, respectively.

Immediate clinical results revealed complete healing of the primary lesions within an average period of twelve and two-tenths days and of the secondary lesions within an average period of seventeen and eight-tenths days.

No serious side effects due to treatment were observed.

In a group of 66 patients followed up for a period of three to twenty-six months, 55 showed satisfactory clinical and serologic progress, 7 underwent infectious clinical relapse and 2 serologic relapse. The serums of 2 patients continued to present positive Wassermann reactions during a prolonged observation period (a rate of failure of 16.6 per cent).

This experimental study was carried out in an attempt to elucidate the problem of the ambulatory treatment of patients with early syphilis with penicillin in water-in-oil emulsion. No definite treatment schedule could be established. However, the treatment of early syphilis with penicillin for depot injection by agents retarding absorption and excretion will ultimately be the method of choice for ambulatory patients.

157 West Fifty-Seventh Street.

8. Jawetz, E.: Dynamics of the Action of Penicillin in Experimental Animals, Arch. Int. Med. **77**:1-15 (Jan.) 1946.

# CHEMISTRY OF PALMAR SWEAT

## VII. Discussion of Studies on Chloride, Urea, Glucose, Uric Acid, Ammonia Nitrogen and Creatinine

WALTER C. LOBITZ JR., M.D.

AND

HAROLD L. MASON, Ph.D.
ROCHESTER, MINN.

THE STUDIES on the concentration of chloride, urea, glucose, uric acid and ammonia nitrogen in palmar sweat[1] were made on pure sweat collected from the openings of sweat ducts on the palmar surface of the finger.[1a] The analytic methods were such that the volumes of sweat collected were adequate for chemical study when the sweat was issuing from the ducts in either a profuse or an intermittent manner (fig. 1 of the article on urea by one of us [W. C. L., Jr.] and Osterberg[1c]): the so-called profuse and intermittent physiologic types of sweating.

In our study on creatinine, it was observed that the volume of sweat which could be collected in the half-hour period of observation in most instances was not sufficient to allow accurate analysis of this constituent even when using the capillary tube colorimetric method of Bordley, Hendrix and Richards[2] adapted to the spectrophotometer by one of us (W. C. L., Jr.) and Osterberg.[3] The analyses

From the Section of Dermatology and Syphilology (Dr. Lobitz) and the Division of Biochemistry (Dr. Mason), Mayo Clinic.

Dr. Lobitz is now in Hanover, N. H.

1. (*a*) Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat; Preliminary Report; Apparatus and Technics, J. Invest. Dermat. **6**:63-73, (Feb). 1945; (*b*) The Chemistry of Palmar Sweat; II. Chloride, Arch. Dermat. & Syph. **56**:462 (Oct.) 1947; (*c*) IV. Urea, ibid. **56**:827 (Dec.) 1947; (*d*) III. Reducing Substances (Glucose), ibid. **58**:819 (Dec.) 1947. (*e*) Lobitz, W. C., Jr., and Mason, H. L.: The Chemistry of Palmar Sweat: Uric Acid, ibid. to be published; (*f*) V. Ammonia Nitrogen, ibid. **57**:69 (Jan.) 1948.

2. Bordley, J.; Hendrix, J. P., and Richards, A. N.: Quantitative Studies of the Composition of Glomerular Urine: XI. The Concentration of Creatinine in Glomerular Urine from Frogs Determined by an Ultramicroadaptation of the Folin Method, J. Biol. Chem. **101**:255-267 (June) 1933.

3. Lobitz, W. C., Jr., and Osterberg, A. E.: Use of the Spectrophotometer in Capillary Tube Colorimetry for the Determination of Reducing Substances (Glucose), Chlorides, Ammonia Nitrogen, Uric Acid and Creatinine, J. Invest. Dermat. **7**:135-144 (June) 1946.

of the concentration of creatinine in palmar sweat, therefore, were limited to studying the normal subjects who were able to secrete an abundant amount of the profuse type of palmar sweat. We had only 2 such normal persons available; both were young women. The information to be gained from these subjects was limited to a determination of (1) the concentration of creatinine in samples of blood and profuse palmar sweat simultaneously collected while the subject was fasting and (2) the effect on the concentration of creatinine in the profuse palmar sweat caused by raising the concentration of this constituent in the blood by the oral administration of 5 Gm. of creatinine. The study was therefore carried out in the same manner as a tolerance test for glucose (figs. 1 and 2).

Within one to two hours after the oral ingestion of the creatinine, the concentration of creatinine in the blood had increased eight to nine times above the fasting level while the concentration of creatinine in the profuse palmar sweat had increased only approximately fourfold above the fasting level. Five hours after the oral administration of the creatinine the concentration of creatinine in both blood and sweat had not returned completely to the original fasting level.

The concentrations of creatinine in thermal-regulating sweat collected from the general body surface or from selected parts of the general body surface have been reported previously[4] as ranging from 0.2 to 12 mg. per hundred cubic centimeters; in the majority of studies the values reported were less than 2 mg. per hundred cubic centimeters.

All that can be concluded from our extremely limited study is that the fasting levels of creatinine in profuse palmar sweat (less than 0.5 and 1.3 mg. per hundred cubic centimeters) seem to agree with the majority of values reported for produse thermal-regulating sweat. In addition, it was observed that when the concentration of creatinine in the blood was elevated the concentration of creatinine in the palmar sweat was also elevated. This elevation seems definite, though slight; the values for palmar sweat never approached the levels of creatinine in the blood.

## COMMENT

This series of studies[1] on the chemistry of palmar sweat was undertaken in an attempt to obtain more information concerning the

4. Mosher, H. H.: Simultaneous Study of Constituents of Urine and Perspiration, J. Biol. Chem. **99**:781-790 (Feb.) 1933. Schumann, R.: Ueber das Vorkommen von Kreatinin und Kreatin im menschlichen Schweisse, Ztschr. f. d. ges. exper. Med. **79**:145-152, 1931. Williams, J. W.: The Pathological Physiology of the Kidneys (and Sweat Glands) in Infections, Urol. & Cutan. Rev. **44**:47-49 (Jan.) 1940. Mickelson, O., and Keys, A.: The Composition of Sweat, with Special Reference to the Vitamins, J. Biol. Chem. **149**:479-490 (Aug.) 1943.

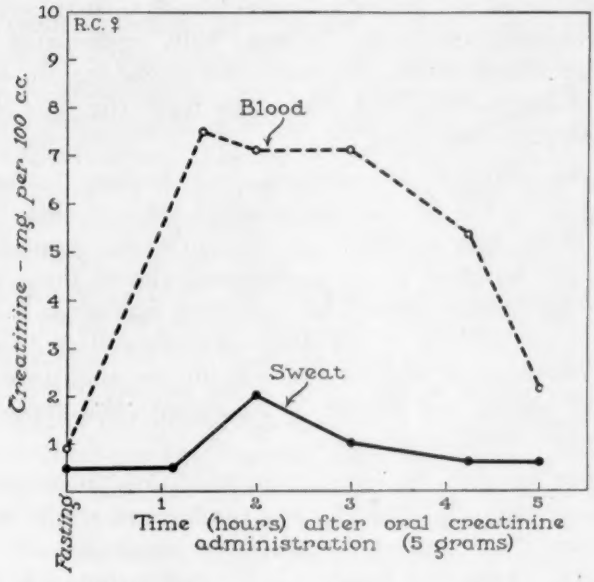



Fig. 1.—The concentration of creatinine in profuse palmar sweat and blood of subject R. C. before and after the oral administration of 5 Gm. of creatinine.

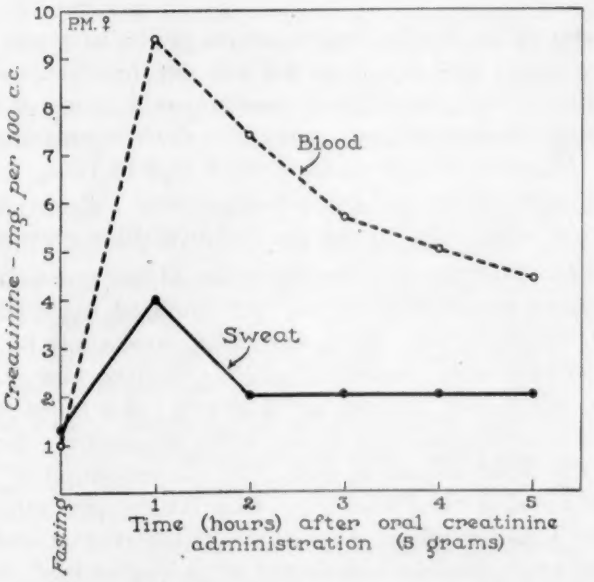



Fig. 2.—The concentration of creatinine in profuse palmar sweat and blood of subject P.M. before and after the oral administration of 5 Gm. of creatinine.

normal function of the individual sweat gland, so that perhaps later its abnormal functions might be more fully appreciated. In most instances differences in the concentrations of the various substances were seen in the two so-called physiologic types (fig. 1 of the article on urea[1c]) of palmar sweating.

The mean value for the concentration of sodium chloride in profuse palmar sweat was 385 mg. per hundred cubic centimeters. When the sweat gland was secreting intermittently the mean value was 1,091 mg. per hundred cubic centimeters, almost three times the mean value for profuse sweat. This value was equivalent to the mean value of sodium chloride in the simultaneously collected urine. The mean concentration of sodium chloride in the simultaneously collected blood plasma was 600 mg. per hundred cubic centimeters for both physiologic types of sweat.

The mean value for the cencentration of urea in profuse palmar sweat[1c] was 68 mg. per hundred cubic centimeters, which was significantly greater than the concentration in simultaneously collected blood (mean: 25 mg. per hundred cubic centimeters). In the intermittent palmar sweat, on the other hand, the mean value for the concentration of urea was 275 mg. per hundred cubic centimeters, or four times the mean concentration in profuse sweat. The concentration of urea in simultaneously collected urine, however, far exceeded that in both types of sweat; its mean value was 1.5 Gm. per hundred cubic centimeters.

The mean value for the concentration of the uric acid[1e] in profuse palmar sweat was less than 0.1 mg. per hundred cubic centimeters, while in the intermittent palmar sweat it was 0.8 mg. per hundred cubic centimeters, or eight times the concentration in profuse sweat. However, the levels in neither type of sweat approached the concentration of uric acid in simultaneously collected blood, the mean value of which was 2.8 mg. per hundred cubic centimeters.

The mean value for the concentration of ammonia nitrogen in profuse palmar sweat[1f] was 7.7 mg. per hundred cubic centimeters. This value was exceeded a little more than three times by the intermittent type of palmar sweat, for which the mean concentration of ammonia nitrogen was 25.7 mg. per hundred cubic centimeters. The latter value approximates the known level of ammonia nitrogen excreted by the renal excreting unit. The concentration of ammonia nitrogen in blood is negligible at less than 0.1 mg. per hundred cubic centimeters. This formation of ammonia by the sweat gland, presumably for the neutralization of acid and the saving of base, presents an interesting parallel with the similar production of ammonia by the kidneys.

The reducing substances (glucose) in both types of palmar sweat[1d] were essentially the same; the mean value in profuse sweat was 3.08 mg. of reducing substances per hundred cubic centimeters and in intermittent sweat 2.86 mg. Whether these values represent glucose is difficult to say. The value of the mode and the median for reducing substances in each type of palmar sweat was 0. The mean value, however, for reducing substances in the simultaneously collected blood was 86 mg. per hundred cubic centimeters.

In addition to these fasting levels for constituents of palmar sweat and blood, this series of studies also revealed that the palmar sweat glands will (1) freely secrete urea when the urea in the blood is elevated,[1e] as do the kidneys, (2) slowly secrete uric acid when the uric acid in the blood is elevated, [1e] as do the kidneys, (3) secrete creatinine when the levels in the blood are elevated, but not as effectively as the kidneys, (4) effectively bar glucose from reaching the surface of the skin when the levels of glucose in the blood are elevated acutely or chronically, while the kidneys are pouring out several grams of glucose in 100 cc. of urine,[1d] and (5) again, effectively produce ammonia nitrogen,[1f] as do the kidneys.

As a guide in these studies, the normally functioning renal excreting unit has been kept in mind. However, the further our studies progressed, the less similar did we find the renal unit and sweat unit to be. This would seem reasonable when one considers that the purpose of the renal unit, speaking broadly, is to remove unnecessary and to conserve necessary chemical constituents of the body. The sweat gland of the general body surface, on the other hand, is primarily a temperature regulator and the function of the palmar sweat gland is, teleologically, to improve tactile sense and the grip on objects.[5]

A diagrammatic drawing of the sweat-secreting unit (fig. 3) shows several of the known unique histologic features that we wish to stress:

1. There are differences in the cellular structure of the coil and duct of the sweat gland.

2. The coil of the sweat gland has smooth muscle fibers about its acinar cells; the duct does not.[6]

3. The coil of the sweat gland receives its arterial blood supply from the deep arterial plexus in the cutis, while the greater portion of the duct receives its blood supply from the subpapillary arterial

5. Darrow, C. W.: Neural Mechanisms Controlling the Palmer Galvanic Skin Reflex and Palmar Sweating: A Consideration of Available Literature, Arch. Neurol & Psychiat. **37**:641-663 (March) 1937.

6. Pinkus, F., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, pt. 1, pp. 300-312.

plexus.[7] The duct preserves its cellular inner lining as it passes through the epidermis[8] and also has a hyalin-like membrane lining its entire lumen.

In a study of the manner of secretion by the sweat gland, Takahara[9] was able to introduce a glass capillary tube into the opening of a palmar sweat duct and observe the movements of the sweat column

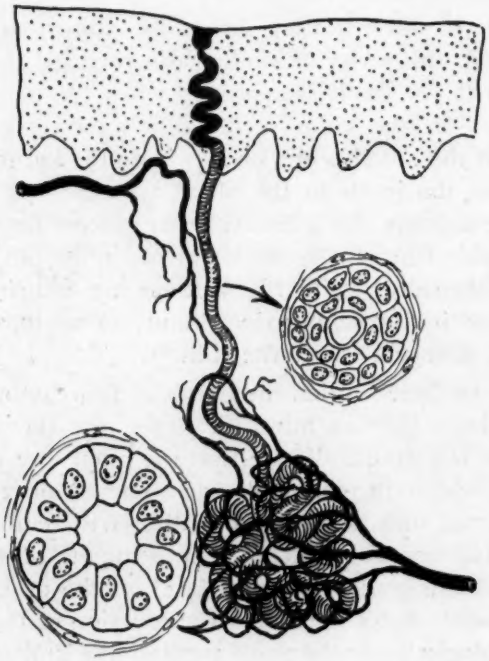


Fig. 3.—Coil and duct of sweat gland, with a cross section of each and their arterial blood supply.

within the tube. His results are shown in figure 4, reproduced from the original tracings. It would seem from these results that even when the sweat gland is at rest the rhythmic contractions of the smooth muscle fibers about the coil cause sweat to rise and fall within the duct, and the longer the sweat gland is not stimulated to secrete, the longer a given volume of sweat is allowed to remain in

7. Spalteholz, W., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, pt. 1, p. 422.

8. Pinkus, H.: Notes on the Anatomy and Pathology of the Skin Appendages: 1. The Wall of the Intra-Epidermal Part of the Sweat Duct, J. Invest. Dermat. **2**:175-186 (Aug.) 1939.

9. Takahara, cited by Kuno, Y.: The Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934, chap. 3, p. 47.

the duct. Figure 4*B* indicates that discharge of sweat is due to a combination of secretion by the gland and contraction of the smooth muscle about the coil of the sweat gland. It has been our experience on many occasions to observe sweat droplets appearing at the openings of the sweat ducts, only to fall back into the duct when the psychic or tactile stimulus was not strong enough to maintain secretion or muscle contraction or both.

Profuse palmar sweat (fig. 1 of the article on urea), then, may be considered to be sweat the passage of which, from the coil of the gland through the duct into the *Sekretbecher* on the palmar cutaneous sur-

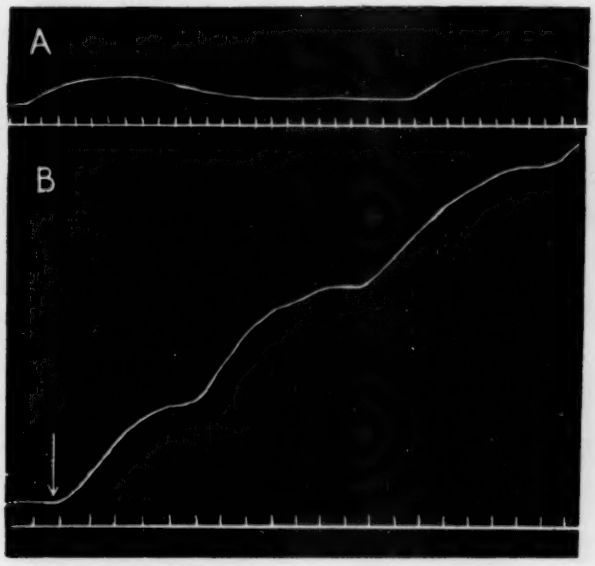



Fig. 4.—*A*, discharge of sweat from a single sweat gland of the palm (secretion at rest). Time marking indicates 5 seconds (Takahara[9]). *B*, discharge of sweat from a single sweat gland of the palm during the grasping of a dynamometer. Time marking indicates 5 seconds (Takahara[9]). (From Kuno, Y.: The Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934.)

face (fig. 5), is continuous and rapid. Intermittent palmar sweat, on the other hand, may be considered to be sweat the passage of which from the coil of the gland to the cutaneous surface is not continuous, but interrupted, so that the sweat remains for varying periods within the duct of the gland.

Since at present it is possible to obtain sweat only from the end of the sweat-secreting unit (fig. 5), and not at any one portion of the unit, one can only speculate as to the reason for the results obtained. The coil of the palmar sweat gland acts either as a filter-

like membrane, imposed between the blood stream and the lumen of the sweat gland coil, or as a selective secretor and perhaps absorber.

The differences between concentrations of the various substances in profuse and intermittent palmar sweat, on the other hand, might occur as the intermittent type of sweat remains in the duct of the sweat gland. One may postulate that the duct (1) may actively and selectively secrete chemicals into the sweat, (2) may merely reabsorb

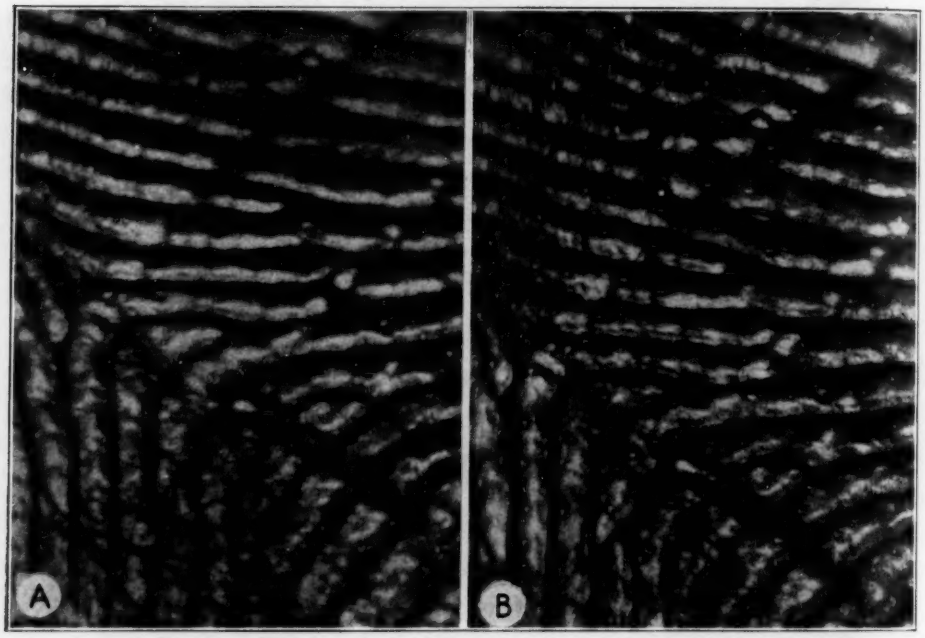



Fig. 5.—*A*, the palmar surface of the nonsweating finger tip (approximately × 20), showing the cup-shaped depressions on the ridges of the finger tip (*Sekretbecher*) into the base of which empties a sweat tubule or duct. *B*, the same area of the palmar finger tip, showing individual glistening sweat droplets, each lying in its *Sekretbecher* immediately after a psychic stimulus. These are the type of sweat droplets that were collected for analysis.

water from the sweat and thus concentrate the intermittent type of sweat more than the profuse type of sweat or (3) may do both. The structure of the duct of the sweat gland, with its hyalin-like tubular lining betwen the double layer of cuboidal cells and the lumen, makes the idea of reabsorption of water in the duct the more plausible of the postulates (no other secreting unit in the body has such a membrane between its secreting cells and its lumen). However, not all the substances studied are concentrated in intermittent palmar

sweat to the same degree. Higher concentrations in intermittent sweat might be due to evaporation during the relatively longer period required for collection of this type of sweat. As was stressed earlier,[1a] evaporation was a constant threat when working with such small volumes of sweat, but repeated checks assured us that evaporation did not occur.

In any event, our results are consistent with the concept that the sweat gland coil secretes certain of the constituents of the blood selectively and that more or less water is reabsorbed by the coil or the duct, or both, depending on the rate of flow.

All these suggestions, however, are merely speculations and are based, for the most part, on evidence that is inconclusive, indirect and as yet incomplete. Not until better methods and better tools are developed will the exact nature of the function of the sweat gland be understood.

## SUMMARY

The fasting levels of creatinine in the palmar sweat of 2 normal women sweating profusely were 1.3 and less than 0.5 mg. per hundred cubic centimeters. The levels of creatinine in the sweat in both cases were raised when the levels of creatinine in the blood were raised above normal by the oral administration of creatinine.

A consideration of the results of the entire series of studies on the chemistry of palmar sweat suggests that the coil of the sweat gland might act as a selective secretor and that the duct or the coil of the sweat gland, or both, may reabsorb water from the sweat.

# Clinical Notes

## STREPTOMYCIN THERAPY FOR CHANCROID

ERNEST JAWETZ, M.D., Ph.D.
SAN FRANCISCO

Mortara and Saito[1] reported recently that streptomycin was effective in treatment for experimental infections of rabbits with Hemophilus ducreyi. Their work suggested a clinical trial of this antibiotic in cases of chancroid. Recently 3 patients suffering from typical chancroid were treated with streptomycin at the United States Marine Hospital in San Francisco. The results of this treatment were so striking as to justify a brief report.

### REPORT OF CASES

CASE 1.—A. S., a 34 year old Negro merchant seaman, entered the hospital with a penile chancre and a tender swelling in the right inguinal region of eighteen days' duration. The patient had always been healthy except for three attacks of gonorrheal urethritis, the last two of which had been treated with "sulfa." The patient remembered that fever and a cutaneous rash appeared when he took "sulfa pills" for the second time. His present illness began with a penile lesion, starting four days after exposure. The ulcer enlarged rapidly, and three days later the patient noticed a tender swelling in the right groin. This grew in size, became painful and interfered with walking.

Physical examination on entry showed a 1 by 1.5 cm. irregular shallow not indurated ulcer, with a necrotic base and surrounded by considerable edema. In the right groin there was tender tense orange-sized swelling, with fluctuation in the center. The temperature was 38 C. (100.4 F.), but though the patient had local discomfort, he did not appear ill. Examination of the blood showed 4,500.000 red blood cells and 14,400 white cells, with a differential count of 82 per cent neutrophils, 3 per cent eosinophils and 15 per cent lymphocytes. The urine was normal. Dark field examinations and serologic tests for syphilis gave negative results. Repeated Ducrey cutaneous tests gave strongly positive reactions: Frei tests elicited negative reactions. Stained smears from the penile lesion showed organisms resembling Hemophilus ducreyi.

With a presumptive diagnosis of chancroid, treatment with streptomycin was started, 0.5 Gm. given intramuscularly every six hours for five days. Fluids were forced, but no other medication was administered. Twenty-four hours after the beginning of streptomycin therapy, the temperature returned to normal. Aspiration of the bubo at that time yielded 12 cc. of thick pus, bacteriologically sterile. The penile lesion improved rapidly and was completely healed eight days after the start of treatment. The inguinal bubo regressed and reabsorbed promptly. No toxic symptoms of any kind were noted. The patient returned to work ten days after admission to the hospital. Examination three weeks lated showed the penile and inguinal scars of the healed lesions, but no evidence of relapse.

CASE 2.—T. S., a 22 year old Swedish seaman, entered the hospital with a penile chancre of two weeks' duration. The patient denied any previous venereal infection and claimed to have always been healthy. Three days after an exposure he noticed a pimple on the penis, which became enlarged and tender and finally

From the United States Marine Hospital, San Francisco.

1. Mortara, F., and Saito, M. T.: Streptomycin in Experimental Chancroid, Am. J. Syph., Gon. & Ven. Dis. **31**:20, 1947.

ulcerated. On admission the only positive physical observations were a soft chancre of the glans penis, measuring 0.5 by 1 cm., with ragged edges and a purulent floor, and bilateral firm walnut-sized tender inguinal lymph nodes. Repeated dark field examinations and serologic tests for syphilis gave negative results. Frei cutaneous tests elicited negative reactions, but the reactions to Ducrey tests were positive with increasing strength. On the basis of a presumptive diagnosis of chancroid, the patient was given streptomycin, 0.5 Gm. intramuscularly every six hours for five days. He experienced no untoward effects. In six days, the penile lesion was completely healed and the lymph nodes decidedly diminished in size.

CASE 3.—P. Q., a 23 year old Puerto Rican sailor, was hospitalized because a large and tender swelling in the left inguinal region made walking exceedingly painful. The patient had always been well in the past. Following a series of exposures, ten days prior to hospitalization, he noticed a small penile ulcer and inguinal adenopathy two days later. On physical examination there was revealed a slightly indurated penile ulcer, measuring 0.3 by 0.8 cm., a walnut-sized tender node in the right inguinal area and a tense fluctuant bubo in the left inguinal region, 12 cm. in diameter. The temperature was 37.9 C. (100.2 F.). Repeated dark field cutaneous tests failed to reveal Treponema pallidum. Reactions to serologic tests for syphilis were doubtful on entry; they later became positive with rising titer. Reactions for Frei cutaneous tests were negative and to Ducrey tests strongly positive, with the formation of local slough. Organisms resembling H. ducreyi were seen in stained smears from the lesion. The impression was of chancroid and early latent syphilis. On a therapeutic regimen of streptomycin, 0.5 Gm. every six hours for five days, the improvement was spectacular. The fever disappeared; the penile lesion closed and epithelized in five days, and after three aspirations of the bubo, which removed 110 cc. of pus, the cavity closed rapidly without any sinus tract formation. Two weeks after the beginning of streptomycin therapy the lesions were all completely healed. The patient subsequently recived 3,400,000 units of penicillin as treatment for latent syphilis.

## COMMENT

The advent of treatment with sulfonamide drugs changed chancroid from a disease of chronicity to one that usually can be controlled in three or four weeks. Unfortunately, the group of sexually most promiscuous patients, that most often contract chancroid, frequently had some other venereal disease treated with sulfonamide drugs in the past. Consequently many of them experienced sensitivity to sulfonamide drugs and could not receive these drugs without serious side effects.

While most patients with chancroid treated with sulfonamide drugs require about one month for the complete healing of lesions, the patients treated with streptomycin reported herein responded much more quickly. These patients were taken at random and happened to represent different degrees of severity of the disease. The follow-up was not sufficiently long to permit judgment of the permanency of cure. If, however, streptomycin therapy can be shown to be equally successful in a larger series of patients with chancroid, then it would appear to be the treatment of choice not only in patients sensitive to sulfonamide drugs but also in many others. The shortening of the illness may well be worth the higher cost of the drug.

The patients reported on were arbitrarily given 10 Gm. of streptomycin in five days. It is entirely possible that a smaller dose may be effective also, and probably injections can be spaced further apart. The results seem sufficiently encouraging in the few patients treated to warrant more extensive clinical valuation.

ADDENDUM.—Since this paper was submitted for publication an article has appeared in the literature comparing the relatively high efficacy of treatment with streptomycin in clearing up chancroidal lesions with the results of treatment with

penicillin and sulfonamide drugs.[2] The authors of that paper used 1 Gm. of streptomycin per day, injected in divided doses every four hours for from seven to twenty-five days. Only a single relapse was observed among 15 patients followed up for sixteen to forty-five weeks.

University of California Medical Center, San Francisco (2).

2. Hirsch, H. L., and Taggart, S. R.: Treatment of Chancroid with Streptomycin, J. Ven. Dis. Inform. **29**:47 (Feb.) 1948.

## DISFIGURING SEQUELAE FROM RADIUM THERAPY

### Results of Treatment of a Birthmark Adjacent to the Breast in a Female Infant

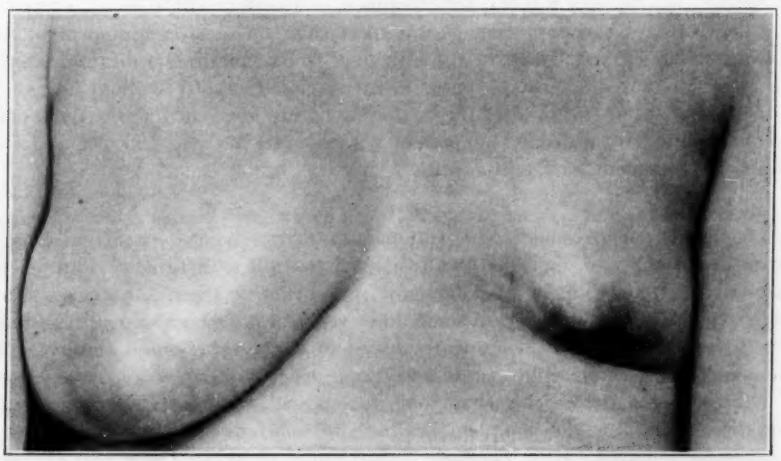
G. B. UNDERWOOD, M.D.

AND

L. EDWARD GAUL, M.D.

EVANSVILLE, IND.

An opportunity was presented to observe G. S., a white girl, aged 12, whom we had recently treated in 1935. Her right breast was mature, but the left breast



Disfigurement of the left breast from radium therapy of a cavernous angioma.

was dwarfed to about one-quarter the normal size. The nipple and areola were not involved. At the medial and inferior border was a linear band devoid of pigment. This area showed no atrophy, induration, telangiectasis or keratosis.

Chagrin attended the review of her record. She had been referred by the family physician when she was 3 months old. At that time, she presented a rapidly growing tumor (duration one month) involving the region of the left breast. The history was not unusual; the infant was developing normally. A dermatologic examination revealed no abnormalities except for an agioma cavernosum, 6 cm. in its greatest diameter, roughly the size of a small apple, topped by a nevus vasculosus, 1 cm. in diameter. The tumor impinged on the inferior border of the breast, but did not involve the areola or the nipple. The parents were apprehensive and insisted on immediate treatment.

On June 29, 1935, 50 mg. of radium, filtered with 1 mm. of brass at a distance of 1 cm., was applied over the tumor for seven hours. Observation on July 29 disclosed no erythema. The tumor had begun to recede. On September 6 the lesion measured 3.5 by 2.5 cm. On October 16 a contact exposure of 25 mg. of radium to each 2 cm. of area, filtered with 1 mm. of brass and 2 mm. of rubber, was applied for two hours. On November 8 regression of the lesion had continued and slight erythema was noticed at the medial border. On November 26, an area of ulceration had appeared at the site of the nevus vasculosus, which healed within the next three weeks. The parents telephoned on December 20, stating that the tumor had disappeared and there was no need for further attention.

MacKee[1] stated that this case is unique in his expereience and represents a lack of glandular development caused by irradiation, in spite of conventional dosage, or a coincidence consisting of congenital lack of development or the angioma involved the gland tissue of the breast in addition to the cutaneous and subcutaneous tissue.

### COMMENT

A warning should be given in all texts concerning possible sequelae after the irradiation of nevi located over, or adjacent to, developing glandular tissues.

509 Hulman Building.

1. MacKee, G. M.: Personal communication to the author.

---

## DIFFERENTIATION OF MICROSPORON AUDOUINI FROM MICROSPORON LANOSUM BY FLUORESCENCE

NORMAN M. O'FARRELL, M.D.
SAN DIEGO, CALIF.

There have recently appeared articles[1] about the "Westinghouse purple X" light and its use as a substitute for the Wood light as a fluorescent agent for tinea capitis. As with any new medicament or physical agent, after enthusiastic welcome and application its limitations quickly begin to appear. The limitations of the "purple X" light give it a clinical use that is of real value, because of the different treatment methods needed for two different fungous infections of the scalp.

The "purple X" light has been hailed as a cheap and simple substitute for the Wood light. In my experience this is not so. The "purple X" light does give fluorescence in infections caused by Microsporon audouini and is entirely adequate for the control examination of that infection. In tinea capitis caused by Microsporon lanosum there will be fluorescence under a Wood light but not under a "purple X" light. Because the former infection usually requires roentgent ray epilation, while local fungicides will cure the infections caused by M. lanosum, this difference in fluorescence gives one a rapid estimate of which treatment method will be required.

I do not consider such a difference to consitute an adequate examination. Cultures are necessary to identify the fungus.

I have had no opportunity to compare the fluorescence of the "purple X" light with the Wood light in tinea capitis caused by other types of organisms than those two mentioned.

1. Dennie, C. C., and Morgan, D. B.: Use of the Purple X Bulb in Diagnosis of Fungus Diseases of the Scalp, Arch. Dermat. & Syph. 55:396 (March) 1947.

# Obituaries

## ARTHUR MOSES GREENWOOD, M.D.

### 1876-1947

Dr. Arthur Moses Greenwood died in Laconia, N. H., on Dec. 14, 1947. He is survived by his wife and two stepsons. He was born in Ashburnham, Mass., March 30, 1876, and had his early education at Cushing Academy in that town. Following graduation at this school he attended Brown University, receiving his A.B. in 1898. His medical education was received at the Harvard Medical School, from which he was graduated in 1902. A surgical internship at the Massachusetts General Hospital, 1902-1904, was followed by an appointment as assistant director of the Massachusetts General Hospital, 1904-1906. From 1906 to 1914 he practiced general medicine in Marblehead. During World War I he served in the Medical Corps of the Army and was at one time in command of an army hospital in France. He was discharged in 1919 with the rank of lieutenant-colonel.

Dr. Greenwood's dermatologic training began at the Vanderbilt Clinic in New York in 1920 and was continued at the Massachusetts General Hospital, where he was appointed to the dermatologic staff in 1921. Here he served until 1937, when he retired and was placed on the Board of Consultation (1937-1947). He was appointed Instructor in Dermatology at the Harvard Medical School in 1925 and served until 1936. He was also Consultant in Dermatology at the New England Deaconess Hospital, the New England Baptist Hospital, Huntington Memorial Hospital, Pondville State Hospital and other hospitals for many years.

He had been a member of the Massachusetts Medical Society and the American Medical Association since he began the practice of medicine. He was elected to the American Dermatological Association in 1928, and he was certified by the American Board of Dermatology and Syphilology in 1933. He was a member of the American Academy of Dermatology and Syphilology and the Society for Investigative Dermatology. He had been a member of the New England Dermatological Society since 1922 and was its president from 1929 to 1931.

Dr. Greenwood's death is a great loss to the dermatologic profession. He had contributed much time and effort to the dermatologic service at the Massachusetts General Hospital. He was an excellent

teacher, and he was a wise and discerning consultant in his special field for many years. He accumulated a wide knowledge of cutaneous disease in its many manifestations. His particular interests were in the fields of malignant disease of the skin and mycology, and his knowledge of the cutaneous manifestations appearing in persons with diabetes was probably unequaled in the country. He was one of the first dermatologists in this part of the country to do special work in medical mycology, particularly the cultural characteristics of various dermatophytes obtained from cutaneous lesions.

A careful observer from his training under Dr. Charles J. White and Dr. F. S. Burns, he was quick to perceive the salient features of dermatologic lesions and to correlate these features with the general picture of the patient's condition. While quiet and unassuming, his carefully considered opinions, based on his keen analysis in the individual case, carried much weight with the patient and with the referring physician.

He made many real friends among his patients and counseled them wisely from his broad background of general medical and special training. Gifted with abundant common sense and with a real ability to sense the practical aspects in a given case, he was a consultant in every sense of the word. His opinions were never obtrusive, and his differences of opinion were often uttered in the form of questions which were vitally related to the particular case which was under discussion. He loved the farm which was his home, and he held a great interest in the marvelous collection of antiques and rare books with which it was filled. His loss is irreparable to his patients, to his medical confreres and to those with whom he worked and was associated for so many years.

C. GUY LANE, M. D.

# News and Comment

## GENERAL NEWS

**Federal Security Agency, Public Health Service.**—The Federal Security Agency, Public Health Service, will give a refresher course for laboratory personnel in laboratory diagnosis of mycotic diseases at the Laboratory Division of the Communicable Disease Center, 291 Peachtree Street, Atlanta, Ga., Aug. 30 to Sept. 24, 1948.

This training is open to all grades of employed laboratory personnel, although first consideration will be given to the laboratories of state and local public health departments; applicants from hospitals and private laboratories will be considered when vacancies occur.

There is no tuition or laboratory fee, but travel and living expenses must be paid by the applicant or his employer. Applications for the course should be made as far in advance as possible. Notification of acceptance from the office of the Chief of the Laboratory Division will be made in sufficient time to allow students to make arrangements for living accommodations. A list of hotels and rooming houses will be sent to applicants at the time of acceptance.

Phases of the program and relative amount of time allotted to each are as follows: (1) identification of common saprophytes (Aspergillus, Penicillium, Cephalosporium, Fusarium, etc.), three days; (2) identification and culturing of the dermatophytes (Trichophyton, Microsporum, Epidermophyton, etc.), five days; (3) identification and culturing of the subcutaneous fungi (Hormodendron, Phialophora, Sporotrichum, Allescheria, Nocardia, Actinomyces, etc.), six days, and (4) identification and culturing of the systemic fungi (Coccidioides, Histoplasma, Blastomyces, Cryptococcus, etc.), six days.

Stress will be placed on practical laboratory procedures useful for establishing a diagnosis of mycotic infection, including: (1) isolation technics, (2) preparation and use of special culture mediums, (3) fermentation reaction tests, (4) vaccine preparation, (5) agglutination and complement fixation tests, (6) inoculation of animals, (7) preparation of permanent mounts and (8) slide cultures.

**Application for Space in Scientific Exhibit.**—Fellows of the American Academy of Dermatology and Syphilology who wish to apply for space in the Scientific Exhibit at the Chicago meeting, Dec. 6, 1948, are requested to write to Dr. Samuel M. Bluefarb, 30 North Michigan Avenue, Chicago 2, Ill., for an application blank.

**Postponement of Tenth International Congress.**—The Tenth International Congress of Dermatology and Syphilology, which was to be held in 1950, has been postponed indefinitely.